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Observations On Pneumococcus Type III Pneumonia*†

By FRANCIS G. BLAKE, A.B., M.D., F.A.C.P., *New Haven, Conn.*

DURING the last two decades there has been a gradually but steadily increasing tendency to classify pneumonia on an etiological basis rather than on the older, anatomical basis of Laënnec; or at least, if the anatomical terms of lobar and bronchopneumonia are retained, to qualify them by an additional etiological diagnosis. This change which has taken place in the classification of pneumonia has undoubtedly occurred because of the increasing recognition of the fact that pneumonia comprises in reality a considerable group of quite different and distinct infectious diseases hitherto all classified under one or the other of two headings—lobar or bronchopneumonia, primarily on the basis of anatomical considerations, but also in part on symptomatology. Etiological differentiation has been particularly emphasized by Cecil¹, and has been ably discussed by Cole² in his DeLamar Lecture of 1927. In one of his concluding paragraphs Cole says, "acute lobar pneumonia due to pneu-

mococcus type I and acute lobar pneumonia due to pneumococcus type II are specific infectious diseases, just as typhoid fever is a specific infectious disease. The other varieties of acute lobar pneumonia are not such well characterized conditions."

Of these other varieties, pneumococcus type III pneumonia has seemed of particular interest for three reasons: first, because it has a very high case fatality rate of 40 to 50 per cent; secondly, because, although highly fatal, it is caused by a type of pneumococcus which apparently leads a harmless, saprophytic existence in the mouths of a considerable proportion of normal, healthy individuals³; and thirdly, because, in spite of this fairly wide distribution of type III pneumococci and consequent frequent opportunity for infection, the incidence of type III pneumonia is usually recorded as being relatively low when compared with that of pneumonia due to type I and to type II pneumococci, organisms which are not found in the mouths of normal individuals except in rare instances³.

Previous studies by Cecil, Baldwin and Larsen⁴ have suggested that these peculiarities of type III pneumonia may be related to its apparently preponderant incidence in the later decades

*From the Department of Internal Medicine, Yale University School of Medicine and the Medical Service of the New Haven Hospital.

†Read at the Baltimore Meeting of the American College of Physicians, March 25, 1931.

of life, frequently in individuals who are the subject of chronic disease, and that in reality the type III pneumococcus is not the highly virulent organism for man which the high mortality of type III pneumonia would seem to indicate.

In an effort to see whether additional information bearing on the foregoing suggestions might be obtained and also to characterize type III pneumonia more definitely as a specific disease, a detailed study has been made of 122 consecutive cases admitted to

group IV cases have not been analyzed, since they have not been classified into the numerous specific types of varied virulence and prevalence included in the group IV pneumococci.

INCIDENCE

The relative incidence of the type III infections is shown in table I and is comparable to that previously reported by others. Of the 606 cases of pneumococcal pneumonia in the series, 122, or 20 per cent, were type III, while type I and type II infections to-

TABLE I
Relative Incidence of Pneumococcus Type I, II, III and IV
Pneumonias, Jan. 1, 1921, to Jan. 1, 1931.

Type	Number	Per Cent	Died	Per Cent
Type I	104	32	45	23.2
Type II	79	13	32	40.5
Type III	122	20	54	44.3
Group IV*	211	35	54	25.6
Total	606	100	185	30.5

*Atypical IIs included with the Group IV cases.

the New Haven Hospital during the ten year period from January 1, 1921, to January 1, 1931. The series includes all type III cases treated on the Medical Service during this period, 104 in number, and 18 cases from the Pediatric Service* admitted since September, 1927, the bacteriological diagnosis of pneumonia on the children's wards not having been carried out before then. For the sake of comparison certain features of the pneumococcus type I and pneumococcus type II pneumonias admitted during the same periods have been studied. The

together numbered 273, or 45 per cent. There were in addition 211 atypical II and group IV cases, or 35 per cent.

The incidence of the type III pneumonias according to age is shown in chart 1. This brings out very clearly the relatively high incidence in the later decades of life. In this series 50 per cent of the cases were 55 years of age or older, while only 15.6 per cent occurred between the ages of 10 and 40. By way of contrast it is shown that the type I and type II cases of this series occurred largely in childhood and early adult life, approximately 50 per cent of the type I cases being under 30 years of age; 87 per cent under 50, while of the type II cases 42 per cent

*I am greatly indebted to Dr. J. D. Trask for the privilege of including the cases from the Pediatric Service.

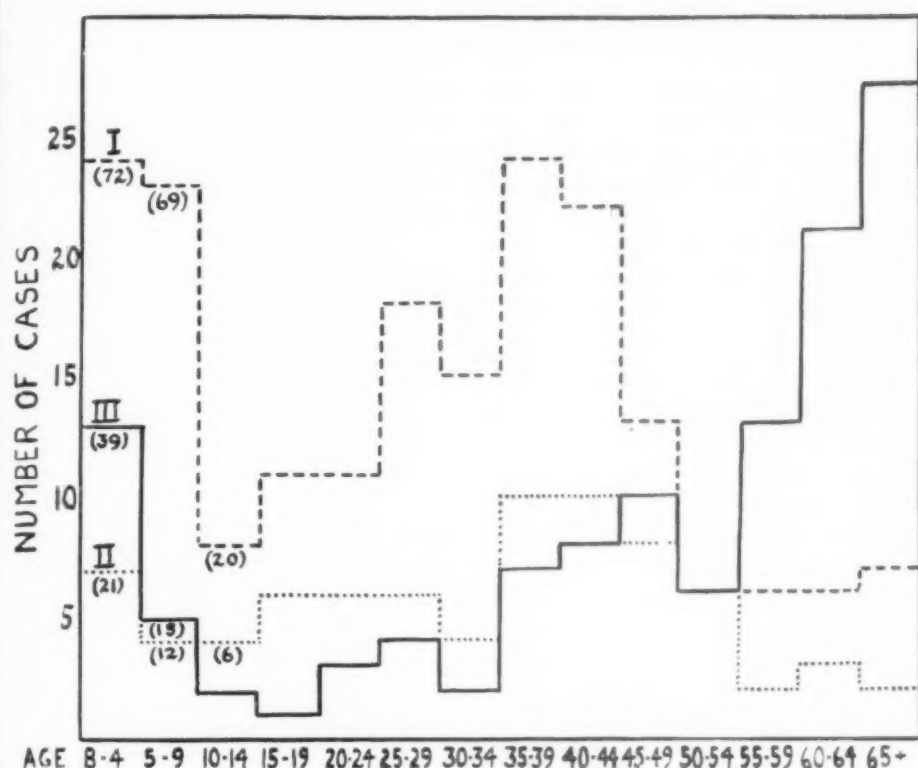


CHART 1. Incidence of pneumococcus type III pneumonia according to age; pneumococcus type I and pneumococcus type II pneumonia included for comparison.

were under 30, 82 per cent under 50. In as much as the cases under 12 years of age occurred during a period of $3\frac{1}{3}$ years and those of 12 years of age or older during a period of 10 years it is obvious that the number of cases in infancy and childhood should be multiplied by 3 in order to approxi-

mate more nearly the actual age distribution. This correction is indicated on chart 1 by the figures in parentheses. The corrected percentages for the different age periods are shown in table 2.

The relative incidence of type I, II, and III infections at different age

TABLE 2
Percentile Incidence of Type III, Type I and Type II
Pneumonia According to Age.

Age	Type III	Type I	Type II
Birth-9	34.2	47.0	32.0
10 - 39	12.0	33.0	36.9
40 - 54	15.2	13.7	24.3
55 +	38.6	6.3	6.8

periods is brought out more clearly in chart 2 from which it will be seen that approximately 70 per cent of the cases over 60 years of age were type III while only 5 to 17 per cent of those between 10 and 40 years of age were type III cases.

The incidence according to sex showed a preponderance of males at all ages, there being 80 cases in males, 42 in females. The incidence according to race showed nothing significant, there being 44 Americans of British ancestry, 20 of Irish descent, 14 of the Hebrew race, 12 Italians, 8 Scandinavians, and 5 Germans. The remainder were of miscellaneous origin.

Incidence and mortality according to months is presented in chart 3. Type III pneumonia does not appear to differ from that due to other types

of pneumococci in its seasonal distribution, the great majority of the cases occurring between October and May, with a very low incidence during the summer. In this series the mortality was higher during the fall and early winter than during the spring.

PREDISPOSING CAUSES

The rôle of acute predisposing causes immediately preceding the onset of type III pneumonia was very high in this series and apparently played an important part in the etiology of the disease at all ages. This is shown in table 3. As would be expected, the acute respiratory infections were outstanding and served as the predisposing cause in 52 per cent of the 115 cases in which information was obtained. Severe exposure, exhaustion and acute

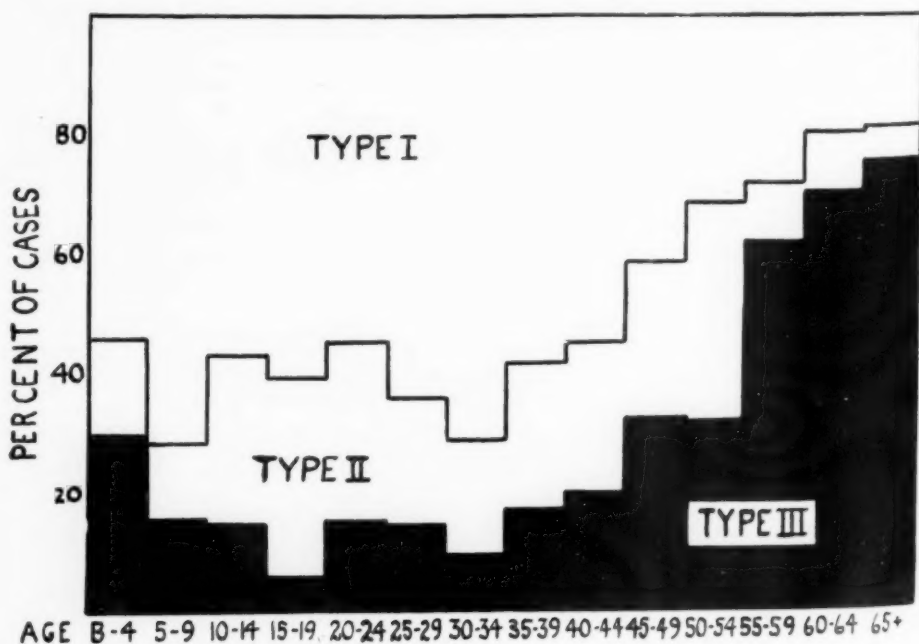


CHART 2. Relative incidence of pneumococcus type I, type II and type III pneumonias according to age.

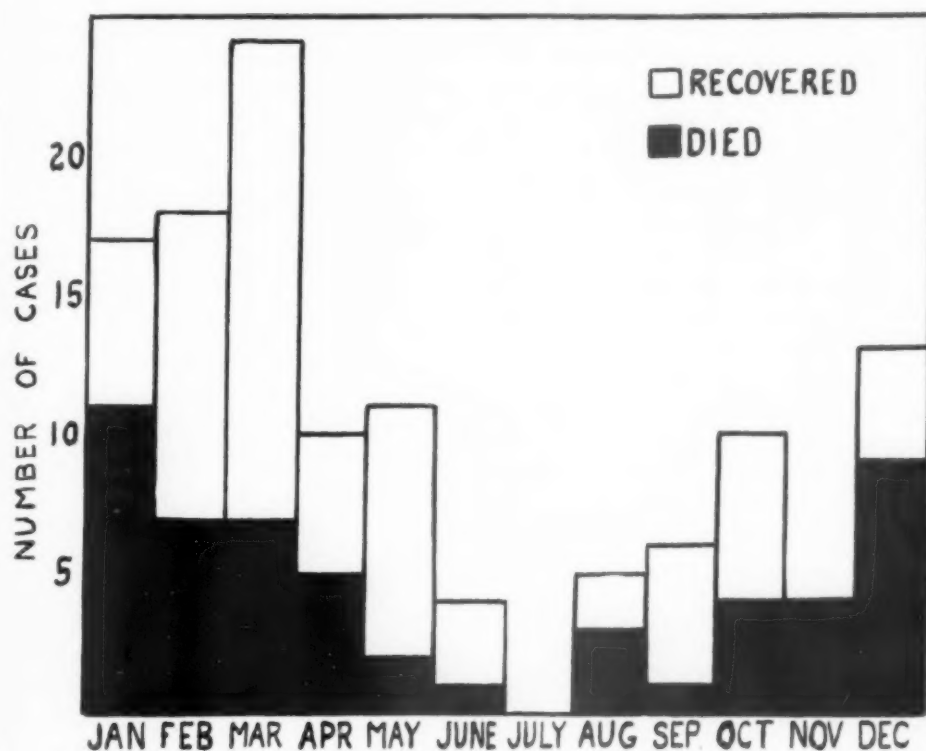


CHART 3. Monthly incidence of pneumococcus type III pneumonia.

TABLE 3
Acute Predisposing Causes in Pneumococcus Type III Pneumonia by Decades.

	B - 9	10 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 +	Total
Common Cold + Exposure + Alcohol	7		3	3	5	6 1	19 1	45
"Grippe" + Exposure + Alcohol				1 1	1	1 1	2	7
Influenza		1	2	2	1	1	1	8
Exposure and Exhaustion					1	2	6	9
Acute Alcoholism					3	1	2	6
Measles	1							1
Pertussis	4							4
Miscellaneous Acute Infections	1	2			3		1	7
Total	13	3	5	7	14	13	32	87
None	5		2	2	2	5	12	28
Undetermined					2	1	4	7

alcoholism also played a considerable part, being recorded as etiological factors in 20 cases. In all an acute predisposing cause was present in 87, or 75 per cent of the 115 cases.

Cecil, Baldwin, and Larsen⁴ called attention to the frequency of chronic diseases in persons who contract type III pneumonia. An analysis of our cases (table 4) amply confirms this. Seventy-nine of the 119 cases in which observations were available, were subject to chronic disease. This might be expected in the patients over 50 years of age, all but 8 of whom suffered from one or more chronic diseases. Of particular interest, however, is the fact that 19 of the 32 patients between 20 and 50 years of age had chronic diseases, if 2 with pregnancy are included; and of these, 12 died, while of the 13 in good health only 2 died, one with influenzal and pneumococcus type III pneumonia, the other of a complicating hemolytic streptococcus infection. To what extent chronic disease acts as a predisposing cause is perhaps uncertain, but that it is an important etiological factor there would seem to be little doubt. Particularly significant is the fact that 32 patients in the series suffered from fairly severe, chronic, pulmonary disease; including bronchial asthma, 5; chronic bronchiectasis, 1; chronic bronchitis usually with emphysema, 25; and advanced tuberculosis, 1. Arteriosclerotic vascular disease, often with heart disease and some degree of heart failure, was present in 39 cases; severe, chronic alcoholism in 11, syphilis in 7, diabetes in 4, and miscellaneous conditions in the remainder. That chronic disease plays an important rôle in the high

mortality of type III pneumonia seems unquestionable. This relationship will be discussed in a subsequent paragraph.

CLINICAL COURSE

The symptoms of onset and the clinical course of type III pneumonia as exhibited in this series of cases showed no conspicuous differences from those found in the other types and will be presented quite briefly. The onset was sudden in 78 cases, the initial symptom or combination of symptoms being chill in 50, pleural pain in 65, vomiting in 31, and convulsions in 4. In 44 the onset was gradual. There was a definite relation between the method of onset and age in that the onset was much more frequently sudden in patients between 10 and 50 (3:1), than in young children and those over 50 (1.5:1). (Table 5.)

The clinical course of the disease presented no unusual characteristics. Sixty-five cases showed pneumonia in one or more lobes of the right lung, of which 34 per cent died; 27 cases showed left-sided involvement, of which 37 per cent died; and 30 cases showed bilateral pneumonia, of which 73 per cent died. (Table 6.)

The duration of the disease in uncomplicated cases varied from 1 to 16 days in those that recovered, over 50 per cent having recovered by the eighth day or earlier; from 4 to 12 days in the fatal cases, 50 per cent having died by the sixth day or earlier and 77 per cent by the seventh day. The relation of age to the duration of the disease and the method of recovery in non-fatal, uncomplicated cases is of interest. (Chart 4.) In the period of lowest incidence and presumably there-

TABLE 5
Method and Symptoms of Onset in Pneumococcus Type III Pneumonia.

Age	Sudden	Gradual	Chill	Pleural Pain	Vomiting	Convulsions
Birth-9	12	7	4	4	8	4
10-29	8	2	4	8	3	-
30-49	19	7	12	15	9	-
50-80	39	28	30	38	11	-
Total	78	44	50	65	31	4

TABLE 6
Extent of Pulmonary Involvement in Pneumococcus
Type III Pneumonia.

Age	Right		Left		Bilateral	
	Rec.	Died	Rec.	Died	Rec.	Died
Birth-9	9		6		2	1
10-19		1	2			
20-29	4		1		1	1
30-39	3	4				2
40-49	8	3	1	2		4
50-59	6	4	2		1	6
60+	13	10	5	8	4	8
Totals	43	22	17	10	8	22
Mortality		34%		37%		73%

DAY OF DISEASE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
B-9				C	C	CC	C	CC	L								
						LL	C	L	L								
10-29		C		CC		CC	CC										
30-49					C	C	C		L		L		L			L	
					LL								L				
50+					L	L	C	L	LL	L	L	L	L		L	L	L
					L		L	L	LL	L		L	L		L	L	
							L		LL								

CHART 4. Duration of disease and method of recovery in uncomplicated, non-fatal cases of pneumococcus type III pneumonia. C = crisis, L = lysis.

fore of greatest resistance, i.e., between 10 and 30 years of age, the cases were clinically mild, of relatively short duration and recovered invariably by crisis. In the two periods showing a somewhat higher incidence and presumably greater susceptibility, i.e., from birth to 10 years and between 30 and 50 years, the duration was somewhat longer and approximately half of the cases recovered by lysis. In the period of high incidence and relatively high susceptibility after the age of 50, the disease was of still longer duration and recovery by crisis very rarely occurred. In fact, after 60, the average duration in 17 cases was 10 days and no case showed a critical recovery. A

glance at chart 4 will show that one should be very hesitant about predicting an early recovery by crisis in patients over 30 with type III pneumonia.

Three factors bearing directly on the debatable question concerning the virulence of type III pneumococcus for man, namely, the frequency and degree of bacteremia, the frequency and severity of pneumococcus complications, and the mortality, are of special interest.

The frequency of positive blood cultures in this series is shown in chart 5 and is compared with the frequency of bacteremia in the type I and type II pneumonias in the series. In the fatal cases bacteremia was consistently less

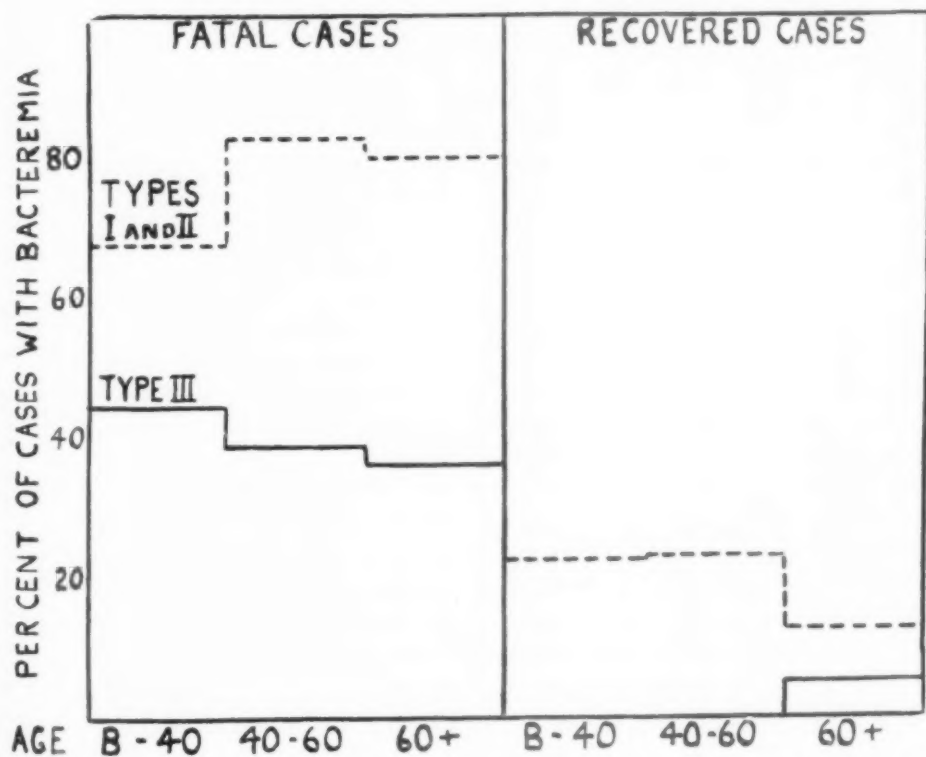


CHART 5. Relative incidence of bacteremia in pneumococcus types I and II pneumonia and pneumococcus type III pneumonia according to age.

frequent in the type III infections than in the Is and IIs. Even more striking is the fact that the frequency becomes progressively lower with advancing age in the type III cases while the reverse is true with the Is and IIs. After 40 only a little over one-third of the fatal type III cases showed positive blood cultures while over 80 per cent of the Is and IIs had bacteremia. A similar contrast is presented in the non-fatal cases, a positive blood culture occurring only once among the type III cases, while positive cultures occurred with considerable frequency in the Is, occasionally in the IIs. It is probable, of course, that the considerable number of type I cases with positive blood cultures who recovered was influenced by serum treatment and that some of the type I pneumonias would otherwise have fallen in the fatal group. At any rate it is quite clear that type III pneumococcus invades the blood relatively infrequently, positive cultures being obtained in only 21, or 18.1 per cent of the 116 cases of type III pneumonia in which cultures were made as contrasted with 71 cases, or 36.6 per cent, with positive blood cultures in the type I series, and 32, or 40.5 per cent, in the type II.

The degree of bacteremia as well as the frequency was relatively slight in the type III infections. In the 21 cases showing positive blood cultures, the 45 cultures made showed 13 with no growth, 9 with growth in broth only, no colonies occurring on the pour plates, 14 with 1 to 10 colonies per cubic centimeter of blood, 5 with 11 to 32 colonies, and only 4 (in 3 patients) showed evidence of a heavy septicemia with more than 100 colonies.

The time of invasion of the blood in the fatal cases is shown in chart 6, first in relation to day of disease in 45 cases in which the day of onset was definitely known; secondly, in relation to days before death in 53 of the 54 fatal cases, no blood culture being made in 1 case. The number of cultures per patient varied from 1 to 5. It is quite clear that bacteremia in the type III pneumonias of this study was in large part a late or terminal invasion rather than an early one.

The occurrence of complications shown to be due or presumably due to pneumococcus infection was not unduly frequent,—otitis media in 5 of the children, empyema in 1 child and in 4 adults, empyema and pericarditis in 1 adult, pericarditis and endocarditis in 1 adult, and thrombophlebitis in 1 adult. Other complications were staphylococcus suppurative parotitis, 1; cystitis (*B.coli*), 2; acute nephritis, 2; pyelonephritis, 1; non-suppurative arthritis, 1; and complicating hemolytic streptococcus infections, 5.

It has been shown in table 1 that the mortality in the series of type III pneumonias was 44.3 per cent, a figure closely comparable to that reported by others. That this high mortality is apparently not due to a highly virulent organism that invades the blood either early or frequently in the disease, nor to an undue prevalence of complications of pneumococcal origin has been brought out. Consequently other explanations must be sought. The first and most obvious reason is that a very large proportion of type III pneumonias occur in the later decades of life. The relation of age to mortality in this series is shown in chart 7, the

figures for the type I and the type II pneumonias being included for comparative purposes. From this data it is at once obvious that in the same age groups type II pneumonia had an equivalent or higher mortality than did type III pneumonia. Furthermore, the

mortality of type I pneumonia, even with serum treatment in the adults, was equivalent to that of type III pneumonia up to the age of 30 and approached it after the age of 45. There would seem to be little doubt from these results that the total high mor-

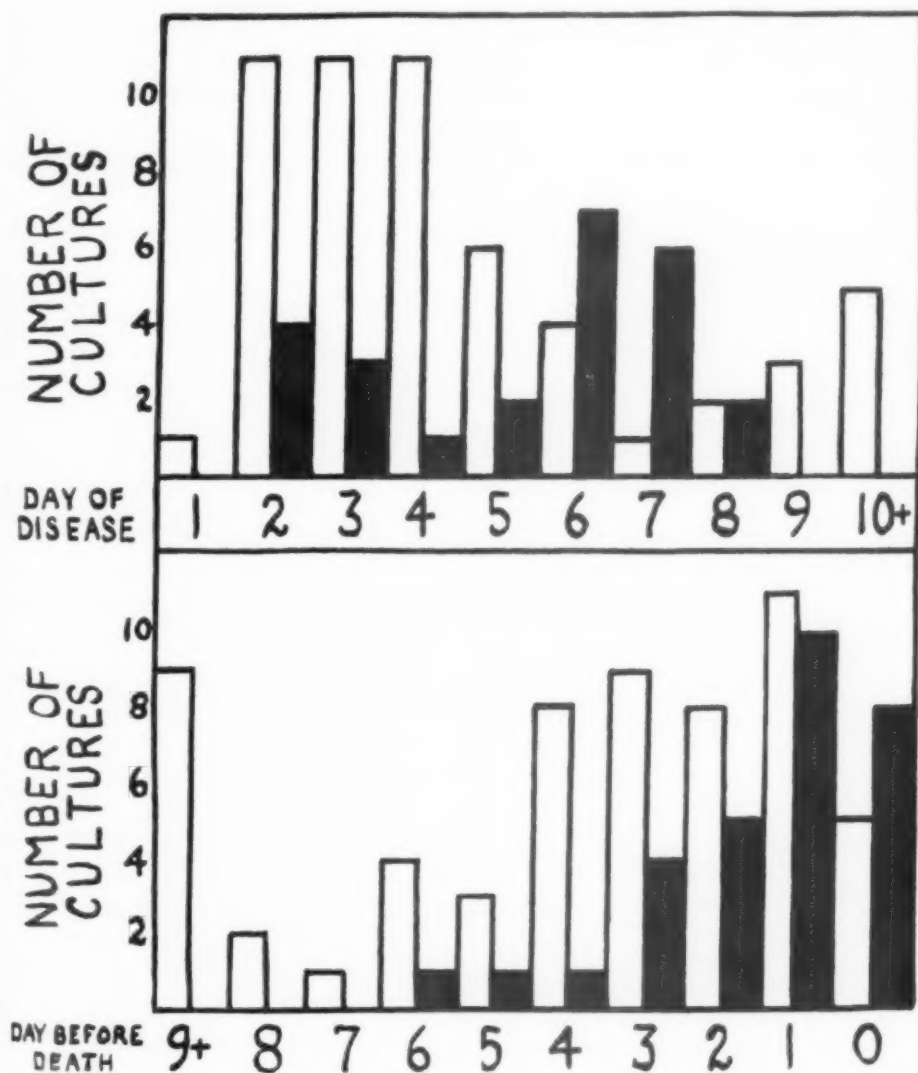


CHART 6. Bacteremia in fatal pneumococcus type III pneumonia in relation to day of disease and to day before death. Solid columns represent number of positive blood cultures, unshaded columns number of negative blood cultures.

tality shown by type III pneumonia is due in large part to the greatly preponderate incidence of the disease in the older age groups, rather than that it is due to an organism of particularly high virulence.

The relation of chronic disease to the high mortality in type III pneumonia has been touched upon above and will be discussed now in more detail. In the first place it will be seen by reference to table 4 that 40 of the 119 cases in which data were available showed no evidence of chronic disease. Of these

only 6, or 15 per cent died, even though 13 of them were over 40 years of age. Of the 6 that died, 1 had a diffuse bronchiolitis (*H. influenzae*) and focal pneumococcus type III pneumonia following whooping cough, 1 really died of agranulocytic angina with a terminal type III pneumonia, 2 had influenzal pneumonia with diffuse bronchiolitis, and 1 died of a complicating hemolytic streptococcus infection which developed 5 days after apparent recovery from the original type III pneumonia, thus leaving only one patient, a man of

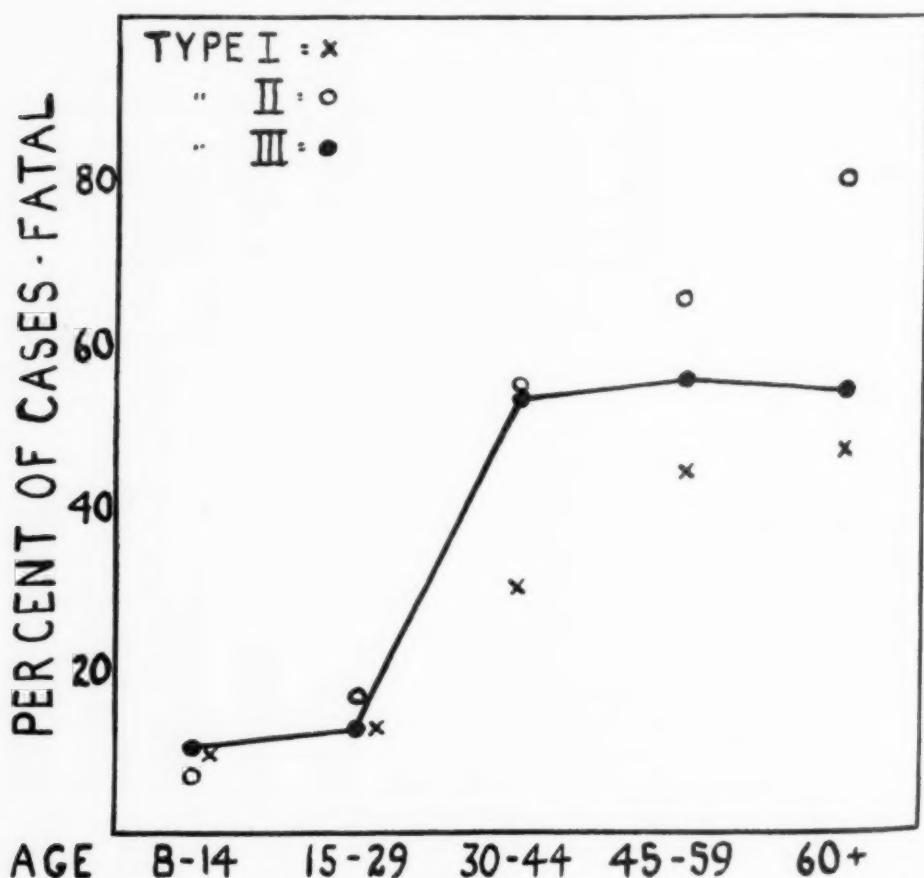


CHART 7. Mortality per cent in pneumococcus type I, in pneumococcus type II, and in pneumococcus type III pneumonia according to age.

59, who died of an uncomplicated type III infection on the ninth day of the disease.

Of particular interest is an analysis of the 9 fatal cases occurring under 40 years of age. The youngest patient was an infant under one year of age with pneumonia following whooping cough. The next was a boy of 14 with agranulocytosis, who developed a type III pneumonia 48 hours before death. The leukocyte count was 1000, with 4 per cent polymorphonuclear cells. The blood culture was positive. The next was a woman of 26 in the ninth month of pregnancy who contracted influenza which was complicated by pneumococcus type III pneumonia. She died on the sixth day. The blood culture was positive. The next was a woman of 31 who had suffered from chronic sinusitis and severe bronchial asthma with chronic bronchitis and emphysema for over a decade. She contracted pneumonia following an acute cold, was admitted on the fourth day of her illness and died on the fifth. The leukocyte count was 35,000, the blood culture negative. The next was a woman of 35 with exophthalmic goiter and syphilis with probable aortitis. She was admitted in a moribund condition and died within 36 hours. The leukocyte count was 58,000, the blood culture negative. The next was a woman of 37 in the third month of pregnancy who had been "sick for two weeks" before the onset of pneumonia. She was admitted on the third day and died on the seventh. The leukocyte count was 19,600, the blood culture negative. The next was a man of 39, a chronic alcoholic with arteriosclerosis and a

fairly marked secondary anemia. Red blood cell count was 3,300,000. Following a "bad attack of grippe" and getting soaked in a rain storm, he developed pneumonia. He was admitted on the second day and died on the seventh. The leukocyte count was 21,400, the blood culture negative. The next was a man of 39 with marked arteriosclerosis. Following a cold he developed pneumonia. He was admitted on the second day with a leukocyte count of 16,200 and a negative blood culture. He developed a marked leukopenia and positive blood culture on the fourth day and died on the fifth. The last was a woman of 39, showing no evidence of chronic disease who had severe influenzal pneumonia with diffuse bronchiolitis. She was admitted on the sixth day with a leukocyte count of 8,800 and a positive blood culture. She died on the ninth day. To continue further with the older patients would be mere repetition and serve no purpose. In order to emphasize the rôle of chronic disease in influencing mortality in this younger group it should be stated by way of contrast that only 4 of the 28 patients who recovered, showed evidence of chronic disease—rickets in a child of 3, chronic nephritis in a boy of 13, bronchial asthma in a boy of 20 and chronic bronchiectasis in a man of 37.

SUMMARY

A consecutive series of 122 cases of pneumococcus type III pneumonia admitted to the New Haven Hospital during the ten year period from Jan. 1, 1921, to Jan. 1, 1931, has been reviewed. Confirmatory of previous reports, it has been found that the inci-

dence is greatest in the later decades of life, approximately 50 per cent of the cases being over 55 years of age. Males were nearly twice as numerous as females. There was no special racial susceptibility found. The monthly incidence corresponded to that of pneumonia in general.

Acute predisposing causes played a very important part in the etiology of the disease, being of undoubted significance in 75 per cent of the cases. The most frequent predisposing causes were the acute respiratory infections—common colds, grippe, and influenza. These immediately preceded the onset of the pneumonia in 52 per cent of the patients. Exposure, exhaustion and acute alcoholism were recorded in 17 per cent. Chronic disease existed in 66 per cent of the patients and in all probability exerted a significant influence on susceptibility. Chronic pulmonary and vascular diseases, and chronic alcoholism were predominant.

The onset, the clinical course and the symptomatology of the disease were similar to those of other forms of pneumococcal pneumonia. In young adult life in otherwise healthy individuals the disease ran a mild course with early critical recovery. In the later decades the disease ran a more prolonged course and recovery by crisis was the exception.

Pneumococcus complications were of the usual frequency. Empyema occurred six times, pericarditis twice and endocarditis once. Otitis media occurred five times in children.

In spite of the high mortality bacteremia was found in only 18.1 per cent of 116 cases, in only 37 per cent of the fatal cases. In the latter it occurred mostly as a terminal invasion 24 to 48 hours before death. In only three cases was a high degree of bacteremia encountered.

Although the total mortality in this series was high, 44.3 per cent, it is shown that this was largely determined by the factor of late age incidence and by the prevalence of chronic disease at all ages in those who succumbed. In 40 cases not subject to chronic disease and irrespective of age, the mortality was only 15 per cent, while in 79 patients suffering from chronic disease (including 2 with pregnancy) the mortality was 56.9 per cent.

Finally, it may be concluded on the basis of the data here presented that pneumococcus type III pneumonia is a highly fatal specific infectious disease due, in general, not to a highly virulent organism that attacks and kills a healthy host, but rather to a debilitated, sickly or senescent host that succumbs to what is a relatively mild and uncommon infection in the young and vigorous.

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Tularemic Pneumonia*†

By H. H. PERMAR, M.D., and W. W. G. MACLACHLAN, M.D.,
Pittsburgh, Pa.

THE literature concerning tularemia became fairly extensive following the publication by Francis^{1,2} (1925-1926), of general articles on the subject, and especially after the papers of Francis and Callender³ (1927), of Goodpasture and House⁴ (1928), of Francis⁵ (1928), and of W. M. Simpson⁶ (1928). The latter articles contributed particularly to the knowledge of pathology of the disease. No attempt will be made here to review the history of tularemia, nor to discuss the literature, save as it concerns tularemic lesions of the lung. The papers of W. M. Simpson^{6,7} (1928-1930), contain excellent summaries of the more recent literature.

The case from which the materials were obtained for this study is, we believe, the twenty-fifth fatal case to be reported in this country, and the ninth to come to autopsy. A peculiar acute pneumonia was the outstanding finding.

CLINICAL HISTORY

The patient was a negro, aged 36, whose last employment had been in cleaning rabbits

for market. On Monday, November 18, 1930, he cleaned a large number of rabbits and the same evening became nauseated and much fatigued. He was forced to leave his work on the following day as he was severely nauseated, although he did not vomit. He was dizzy and very weak. Later in the day he had a chill, was feverish and had a severe headache. He went to bed and remained there in this state until brought into the hospital on Saturday, November 23, 1930, the fifth day after the onset of symptoms.

On admission the patient appeared to be very toxic; the temperature was 105°F., the pulse 100, the respirations 28. There was some soreness in the right axilla but no enlarged glands were felt. A number of small, superficial cuts were noted on the palmar surface of the right hand, but there were no ulcers. The lungs were clear, although the case was considered at first as a possible pneumonia. The heart was normal. The blood pressure was 120/80; the pulse rate was relatively slow. The spleen was not palpable. The white cells were 7,125, with polymorphonuclear leucocytes, 47 per cent; large lymphocytes, 22 per cent; small lymphocytes, 23 per cent; large mononuclear leucocytes, 8 per cent. The urine was not remarkable. The blood culture was negative. On account of the history of contact with rabbits, blood was sent to Dr. Edward Francis at Washington shortly after admission (seventh day of the disease); and the report was, "No agglutination with *B. tularensis*". The subsequent points of interest in the clinical course were as follows: delirium which was almost constant, incontinence of urine and feces, and continued high fever, with relatively slow pulse and respiratory

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†Read before the Cleveland Meeting of the American Association of Pathologists and Bacteriologists, April 2, 1931.

rates. No cough or sputum was present although the patient said he spat up a little blood during the first few days of illness. There were no physical signs of pneumonia until two days prior to death (fifteenth day of the disease), when signs of consolidation were noted on the right side anteriorly, over the upper lobe. Hiccough was very persistent. The Wassermann test on the blood was negative. A later blood count (seventeenth day of disease) showed only 5,200 leucocytes, with polymorphonuclear leucocytes, 84 per cent; lymphocytes, 14 per cent; large mononuclear leucocytes, 2 per cent. There was no subsequent lymph-node enlargement, and on the seventeenth day of his disease blood was again sent to Dr. Edward Francis, who reported a positive agglutination (1:320) with *B. tularensis*. The patient died on the seventeenth day of his illness.

Autopsy

The outstanding autopsy findings were confined almost entirely to the lung, though typical tularemic lesions were also found in the peribronchial lymph-nodes and in the liver. The external appearance of the body offered nothing, save that the palms showed a few healing scratches. The axillary glands were not palpable.

Thorax. The thorax showed voluminous lungs and some pleural adhesions. There was only a slight acute pleural exudate, largely confined to the involved right lung, and chiefly to the right upper lobe, the site of the pneumonia.

The left lung weighed 350 gms., and the right, 950 gms. The lungs presented pleural adhesions, anthracosis and, in both apices, small old tuberculous scars. Both had some edema and congestion, especially in their lower lobes, and more intense in the right lung, the upper lobe of which felt firm and solid. The pleural surface of the right upper lobe was dulled by a film of yellow opaque fibrin, beneath which the interlobular divisions were evident as slightly elevated yellowish lines. On section, the tissue was generally consolidated, though the exudate was much denser along the bronchial tree, especially about the bronchioles and along the interlobular septa. The latter could be seen as opaque lines and they were most evident

in the peripheral parts of the lobe. Some of these lines were quite wide, and so edematous as actually to appear spongy or cystic in the gross. The bronchi, especially the smaller branches, were surrounded by dense, opaque, yellow-white, necrotic-looking areas which merged with the usual black peribronchial markings of anthracosis. The necrotic peribronchial foci were connected by consolidated lung which varied in color and consistency, but which in general had the gross character of gray hepatization. The bronchial tree contained a mucopurulent material that appeared thicker in the finer bronchioles. The larger vessels were clear. Thrombi were not seen on gross examination. The peribronchial lymph nodes showed slight enlargement and marked anthracosis. Their important lesion consisted of small white nodules of necrosis, with no fibrosis about them. There was also in one of the nodes a small area of caseation surrounded by fibrous tissue and showing a little calcification. No other nodes in the thorax or abdomen were found enlarged or similarly involved. The heart and pericardial sac revealed nothing abnormal. The aorta showed only a few superficial fatty streakings.

Abdomen. The peritoneal cavity had no abnormalities. The liver weighed 2,050 gms., and was the only abdominal organ showing notable change. Five or six tiny, pin-head sized, gray-white areas were found beneath the capsule, with neither fibrosis nor congestion about them. They had a depressed surface and appeared as small, clearly marked foci of necrosis of the liver substance; this appearance was borne out on cross section. No additional nodules were found on the cut surface of the liver. These lesions in the liver resembled those in the peribronchial lymph-nodes. In addition, the liver and kidney had undergone definite cloudy swelling. The spleen was congested and showed a typical recent white infarct.

The brain was not examined.

The heart's blood was sterile. No cultures were made from the lung. Direct smears showed moderate numbers of polymorphonuclear leucocytes, many mononuclear cells often containing carbon granules, and much amorphous debris. No bacteria of any type could be demonstrated in the smears by

ordinary methods, and Ziehl-Neelsen stains showed no acid-fast organisms. No animal injection of tissues was done. The serum obtained on the seventh and seventeenth days of illness was injected into guinea pigs by Dr. Francis, with negative results.

Microscopical Findings

The microscopic changes in the lung, peribronchial lymph-nodes and liver were of particular interest. These organs all showed miliary foci of necrosis, identical with those found in animals and in acutely fatal human cases.

The sections of the involved portion of the lung presented typical miliary necrotic foci in the interstitial tissues. Certain of these lay in the walls of lymphatics, though as a rule they were simply scattered in the

stroma about the bronchial tree and vessels. The interstitial tissues were also the seat of an intense acute inflammation, characterized by extreme edema with much fibrin formation and a cellular exudate made up chiefly of large mononuclear leucocytes. The alveoli were extensively and diffusely involved in a pneumonia of serous and serofibrinous type. The predominating cell in the alveolar exudate was again the large mononuclear leucocyte. These cells tended to crowd the alveolar spaces and to become degenerated and necrotic; and the alveoli containing necrotic exudate also showed numbers of polymorphonuclear leucocytes. The characteristics of the mononuclear phagocytes which everywhere predominated in the cellular exudate were worthy of note. In the edematous interstitial tissues, in the

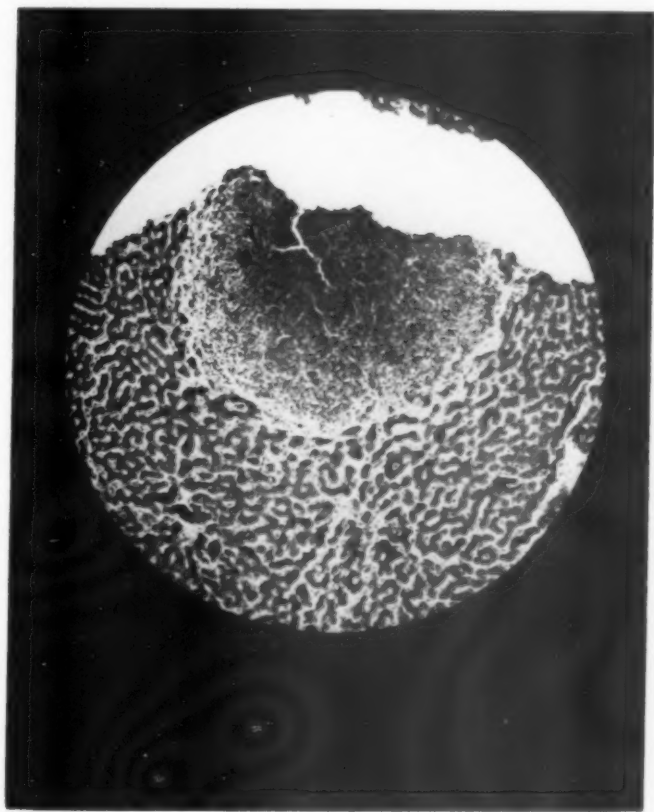


FIG. 1. Typical acute miliary tularemic lesion of liver.

dilated lymphatics, and in the adventitial and subendothelial zones of the vessels, they had generally a smaller size, with hyaline cytoplasm and a 'clock face' arrangement of the chromatin in the relatively large, eccentric nucleus. In a word, many resembled plasma cells, though all gradations could be found between these and typical mononuclear phagocytes. When they appeared free in the alveoli they were greatly enlarged, with foamy, vacuolated cytoplasm and relatively smaller nuclei that were often pyknotic. In the alveoli their phagocytic properties were most evident. They nearly all contained fragments of chromatin, lipoid materials, degenerating erythrocytes, and varied quantities of carbon granules. The alveolar lining cells were swollen and quite prominent in the alveoli containing serous fluid and few inflammatory cells. They were less evident

where the exudate was more massive. It did not appear that the alveolar epithelium had desquamated to any appreciable degree.

Areas of necrosis of large groups of alveoli were a distinctive feature of the pneumonia. The necrosis involved the alveolar walls as well as the contained exudate. This change was the result of a striking lesion, involving both venules and arterioles and consisting of an acute inflammatory reaction of the subendothelial connective tissue with marked edema and swelling and an infiltration by mononuclear leucocytes. This, of course, resulted in great narrowing of the lumina; and as thrombosis tended to occur in many of the narrowed vessels, extensive necrosis of the lung tissue was inevitable. A similar but less marked change was present in the adventitia. These vascular lesions

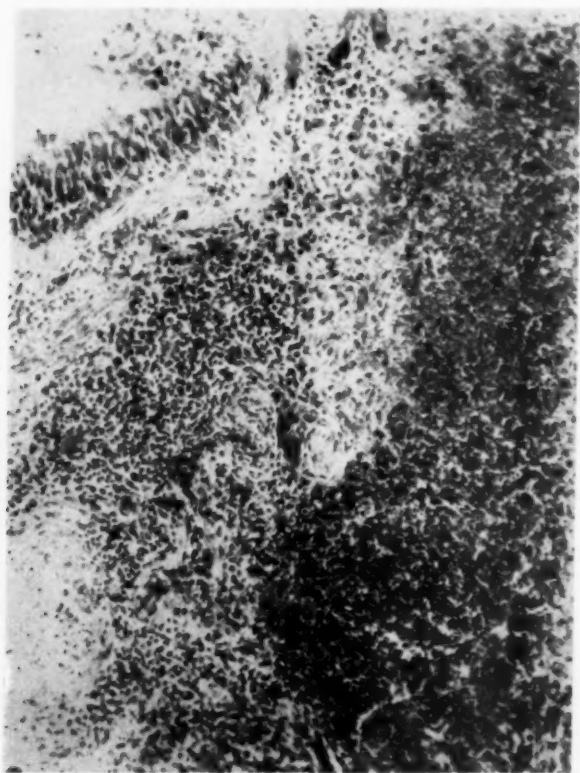


FIG. 2. Miliary necrotic tularemic foci in wall of bronchus. Note interstitial edema and inflammatory exudate.

were found only in the lobe showing pneumonia.

The bronchial tree itself was affected particularly in the finer branches. Here the lumina contained masses of exudate like that in the alveoli, made up of mononuclear leucocytes, coagulated serum, fibrin and polymorphonuclear leucocytes. This exudate showed a tendency to necrosis, as did that in the alveoli. The mucosal linings of some of the bronchioles showed localized acute inflammation and even necrosis, which appeared to be a progression from the miliary necrotic foci in their interstitial tissues. It was noted that the mucosa of the larger bronchi revealed much less injury and exudate. The inflammatory reaction in the interstitial tissues was the outstanding feature of the reaction, while that in the bronchial tree was a

minor one, occurring by direct extension from the wall into the lumen.

The sections of the small focal liver lesions and of the similar but somewhat larger necrotic lesions of the peribronchial lymph nodes presented the characteristic acute necrotizing process that has been described by Verbrycke⁸, Francis and Callender³ and others, and therefore does not require elaboration here.

The infarct of the spleen gave the typical microscopic picture of a white infarct. This was in all likelihood the result of embolism from a pulmonary thrombus. No vascular lesions like those in the pneumonic lung were found in the spleen or other organs.

Fat stains (Sudan III) demonstrated moderate amounts of neutral fat in fine globules in the wandering mononuclear cells

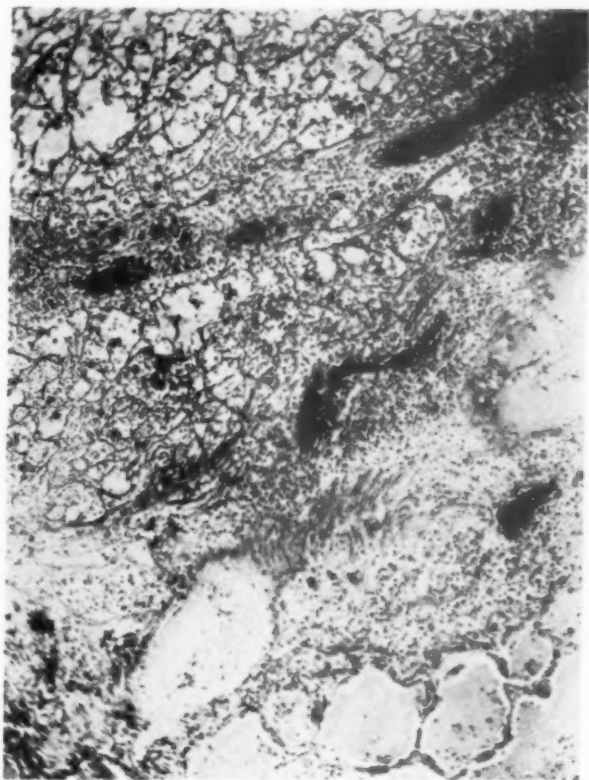


FIG. 3. Extreme edema of stroma with fibrinous and mononuclear cellular exudate, and serous exudate in alveoli.

of the exudate, notably in the necrotic exudate. This was true in all the tularemic lesions, whether in lung, liver, or lymph nodes at the hilus of lung; but the striking fatty changes described by Palmer and Hansmann⁹ were not evident in the other organs. Controlled Ziehl-Neelsen stains on lung tissue showed no acid-fast organisms. Gram-Weigert and Giemsa stains for bacteria in the lung tissues revealed no organisms. The Brown-Brenn stain, which is especially useful for Gram-negative bacteria, showed no Gram-negative organisms, and no evidence of secondary infection.

DISCUSSION

The literature contains published reports of eight autopsies on fatal tularemia. In Francis' case¹⁰, the chest was

not prosected, though there was clinically a pneumonia. Verbrycke⁸ reported in the lungs typical acute tularemic nodules, the size of small shot, and one the size of a walnut. These had an associated bronchopneumonia in adjoining alveoli and bronchioles. Bardon and Berdez¹¹ described small necrotic patches involving several alveoli. The septal walls were necrotic. The necrosis resembled that of tuberculosis. Palmer and Hansmann's⁹ case presented what they termed an "inconsiderable" bronchopneumonia, but they noted unusual numbers of vacuolated mononuclear cells in the smaller vessels and wan-

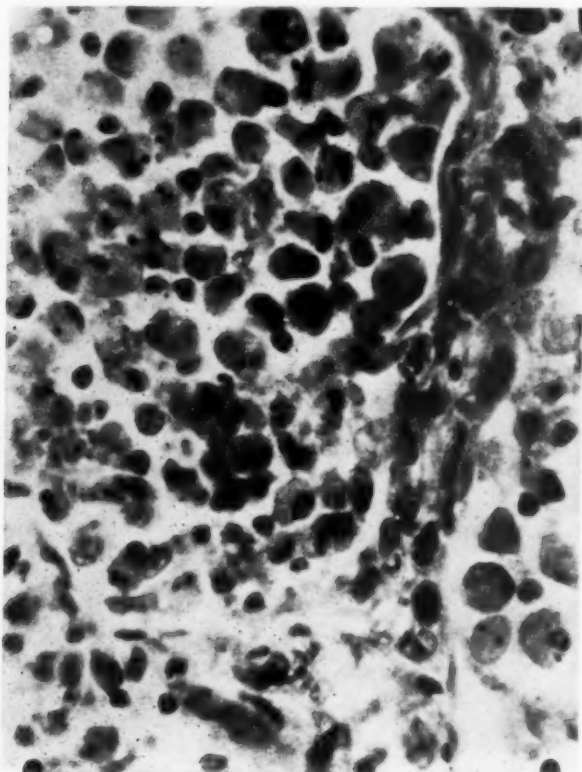


FIG. 4. Mononuclear phagocytic cells in the alveolar exudate.

dering into the alveoli. Bunker and Smith¹² found a marked bronchopneumonia, with extensive necrosis of the alveolar walls as well as of the free exudate. The cellular exudate consisted chiefly of polymorphonuclear leucocytes, though many lymphocytes and endothelial cells were present. The peribronchial lymph-nodes in all the foregoing were reported as showing typical tularemic granulomatous foci, in either the acute or the sub-acute stage. W. M. Simpson's⁶ case, the most acute to come to autopsy, had no pneumonia, but two typical

acute tularemic nodules were found in the lung tissue. The case of Goodpasture and House⁴ showed only a localized pleurisy with a mononuclear cell exudate, near the enlarged peribronchial lymph-nodes. In Bruecken's³ case (in which the patient had recovered from a pneumonia in the early weeks of the disease), the lungs were found clear at autopsy when death from chronic glandular tularemia finally occurred five months after the onset.

In brief then, seven out of the eight cases in which the thorax was prosected (87.5 per cent) presented

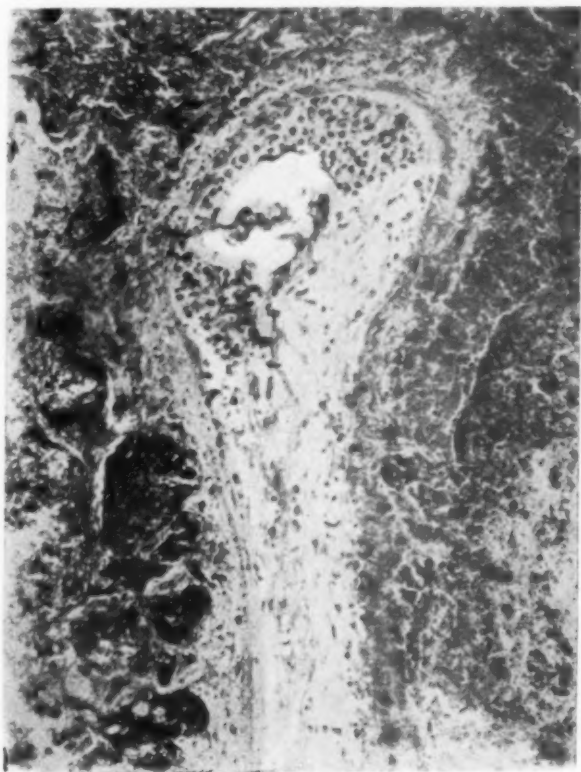


FIG. 5. Subendothelial edema and mononuclear cellular exudate in intima of pulmonary vessel. Serous and fibrinous exudate in adjoining alveoli, with necrosis of lung tissue and the contained exudate.

tularemic lesions of some type in the lung; and in five of the eight (62.5 per cent) there was diffuse pneumonic involvement. Of all the reported fatal cases, now numbering twenty-five, nine (36 per cent) showed pneumonia either clinically or at autopsy.

The present case report indicates that an infection by *B. tularensis* occurred without demonstrable localized granulomatous ulceration on the skin and without regional lymphatic involvement. In the absence of peripheral localized tularemic lesions in either

the skin or lymphatics, one must consider here the possibility of primary respiratory tract infection, with direct interstitial invasion of the lung. The mode of infection of the lung cannot be determined from the data available, but the case is of value since it gives an opportunity to describe in detail the pulmonary lesions.

The presence in the stroma of the lung of the typical miliary necrotic focal lesion is the most significant single finding, from the standpoint of identifying the pneumonia as of tulare-

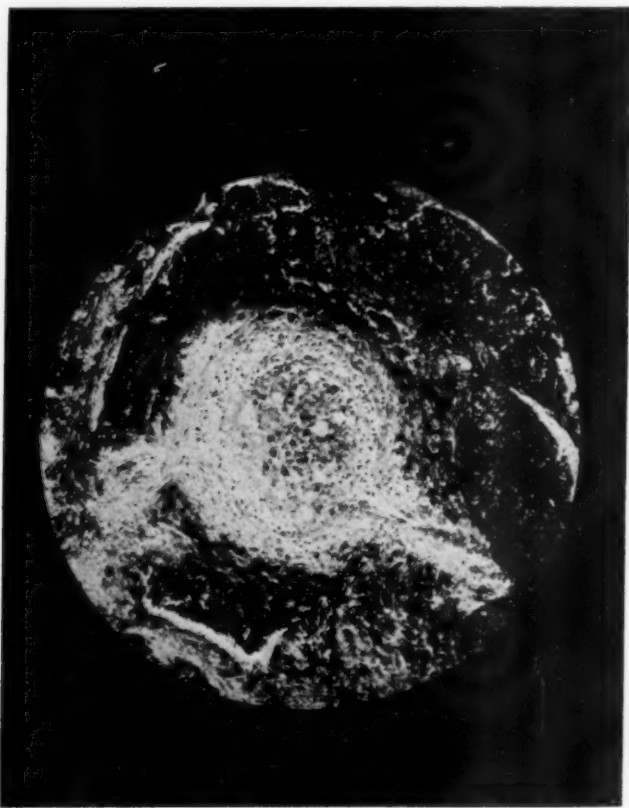


FIG. 6. Thrombosis of pulmonary vessel showing subendothelial edema and mononuclear cellular exudate. Necrosis of the surrounding lung alveoli and the contained sero-fibrinous exudate.

mic origin. The other outstanding feature is the extreme subendothelial edema and mononuclear cellular infiltration in the blood vessels. This latter observation has not been recorded previously. It is of considerable interest, as we believe this vascular lesion with the associated thrombosis in the affected vessels, explains the peculiar necrosis that has been noted in tularemic lung inflammations. The usual proliferative and obliterative changes in the smaller vessels and capillaries, which were first described in tularemic lesions in the human by

one of us (Permar and Weil¹²), and subsequently by Francis and Callender³, and others, are not present, probably because of the rapidly fatal course of the disease. The predominance of mononuclear leucocytes in the cellular exudate is evident in this case, as in most of those previously described.

We believe that we have demonstrated a pneumonia with morphologic changes which are presumably specific for tularemia and recognizable with reasonable certainty in the absence of a suggestive history or of a positive agglutination test. It is of course to

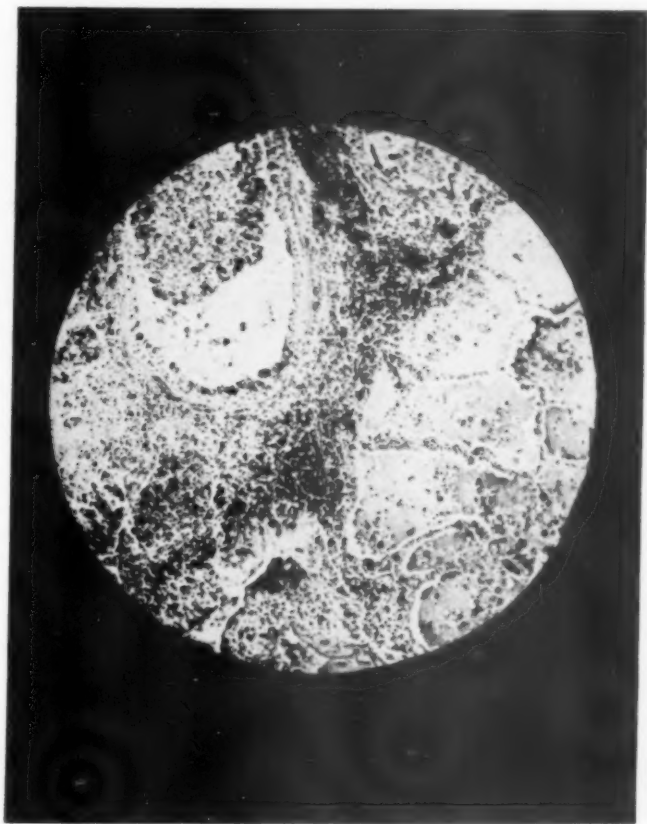


FIG. 7. Small bronchiole with a mononuclear cellular exudate. A more active process present in the surrounding lung tissue.

be kept in mind that the duration of the disease may well alter somewhat certain phases of the microscopic reaction. Further, we are not aware of a pulmonary inflammation occurring in any other infectious disease that has exactly the characters described here.

As to the clinical importance of lung involvement in tularemia, we agree with Francis^{6,11} who has stated that a pulmonary lesion indicates a serious prognosis. This is borne out by the high incidence of pneumonia in fatal cases. We would emphasize that the history of contact with carriers of *B. tularensis* (most commonly wild rab-

bids), is very important in the diagnosis and further, that the agglutination test is necessary for absolute confirmation. It must be kept in mind, as indicated by this case, that a positive agglutination test may not be developed early in the disease.

SUMMARY

The case of tularemia which forms the basis of this report was remarkable in that there was neither a peripheral ulcerative lesion nor regional lymphadenitis. The outstanding clinical manifestations were a markedly toxic state and an atypical pneumonia.

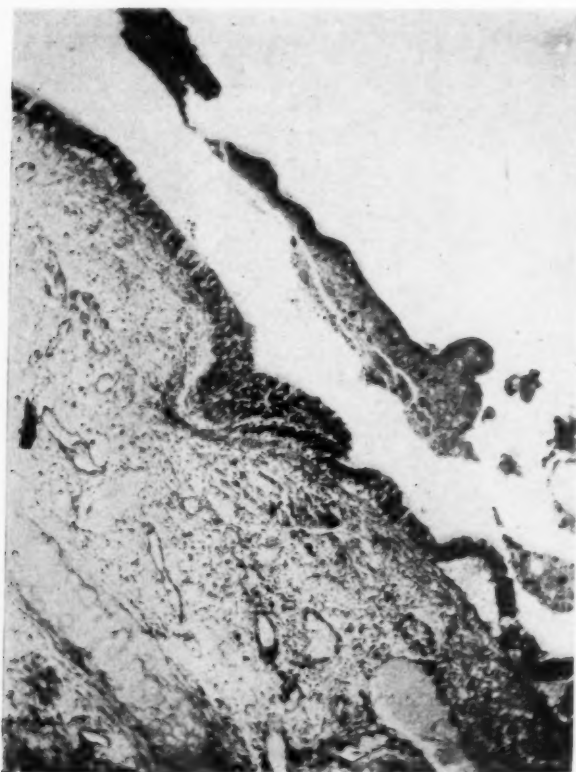


FIG. 8. Large bronchiole with the wall intact, and containing a little serous exudate and a few mononuclear phagocytes.

Tularemia was suggested by the history of handling dead wild rabbits and was confirmed by a positive agglutination test for *B. tularensis* on the patient's blood serum.

At autopsy, the gross findings in the lung were unusual, indicating an acute lobar pneumonia with much interstitial inflammation and necrosis. The lesion suggested an acute diffuse reaction of granulomatous type.

The histopathologic lesion was essentially an interstitial pneumonia, distinguished by multiple miliary necrotic foci throughout the stroma of the diseased lobe. These necrotic foci were identical with those seen in an acute diffuse tularemic infection. An intense and widespread inflammatory edema accompanied the development of the specific tularemic nodules in the lung. The blood vessels of the affected lobe showed great edema of the subendothelial and adventitial connective tissue, with an infiltration of mononuclear leucocytes into these coats. This involvement of the vessels produced much narrowing of their lumina, and complete occlusion by thrombosis was often found. Areas of necrosis of considerable size and irregular outline

were a striking feature of the microscopical findings. This necrosis was associated clearly with the vascular lesions just described, and appeared to have been caused directly by the vascular narrowing and occlusion.

Thus it may be stated that when a diffuse pulmonary involvement occurs in the course of a tularemic infection, the prognosis must be grave, as acute tularemic inflammation of the lung is a progressively destructive lesion. This is borne out by the data available on fatal tularemia.

The authors take pleasure in availing themselves of this opportunity to express their thanks to Doctor John M. Johnston of Pittsburgh for his kind assistance in the preparation of the microphotographs illustrating this paper.

Since this paper was written, the authors have learned from Dr. Edward Francis of the Public Health Service, National Institute of Health, Washington, D. C., that four other autopsy reports, two with prominent lung lesions, are in process of publication; and Hartman of Detroit reported before the American Association of Pathologists and Bacteriologists, April 2, 1931, an autopsy on tularemia with interstitial tularemic pneumonia among the findings. These cases add somewhat to the evidence that pulmonic tularemia has a grave prognosis.

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Experimentally Produced Lesions of the Liver*†

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MANY problems of clinical medicine have been clarified by experimentation on animals. This method has numerous advantages in that most of the factors which enter into the production and progression of abnormal processes are capable of exact control. Although it is not as yet possible exactly to simulate in animals all of the types and phases of hepatic disorders, it is possible to produce experimentally most of the abnormal conditions usually associated with hepatic disease in human beings. With our associates we have studied a large number of animals following various procedures which have directly affected the liver, and it is from these animals that we have drawn our conclusions concerning the physiology and pathology of the liver.

Perhaps our most valuable data have been obtained from animals following complete removal of the liver,^{2,4,6,7,9,11,12,14,15,20,21} but since most of the facts of this series are well known, only brief mention of them will be given here. After proper preliminary measures to eliminate complicating factors

such as portal stasis, the liver may be completely removed and the signs of complete hepatic insufficiency may be observed. Because the liver alone adds glucose to the blood, hypoglycemia is the first definite symptom referable to the absence of the liver. Fortunately, in the human being only the rare case of extreme acute atrophy of the liver presents this symptom. If hypoglycemia is prevented by the administration of glucose the liverless animal presents no unusual symptoms for twenty-four to forty-eight hours, at which time a characteristic set of symptoms develops and death from complete hepatic insufficiency follows. These symptoms are loss of hearing, loss of vision, loss of reflexes, muscular rigidity, coma, convulsions, and death, progressively occurring in the order mentioned; the entire course usually lasts from thirty minutes to four hours. We know of no hepatic disease in which these symptoms are exactly reproduced, although several of them are noted in fatal cases of supposed hepatic insufficiency. In addition to loss of the power of forming sugar, the liverless animal also loses the power of forming urea, of destroying amino acid and uric acid, and of effecting other metabolic changes for which the liver is essential.

*Read at the Baltimore Meeting of the American College of Physicians, March 23 to 27, 1931.

†From the Division of Experimental Surgery and Pathology, The Mayo Foundation, Rochester, Minnesota.

It would appear that any test⁸ capable of measuring the metabolic changes which depend entirely on the liver would give an accurate index of the efficiency of this organ. There are several reasons why such tests show but little, and studies of animals from which the liver has been partially removed reveal some of the reasons for failure of these tests. In the dog, and in many other animals, the liver consists of several distinct lobes, one or more of which may be successfully removed. Immediately following such operations the remaining portions of the liver begin to hypertrophy and by serial operations, removing a lobe of liver every few weeks, it is possible to remove more hepatic tissue than was originally present and still have a normal weight of hepatic tissue remaining in the dog. Even the liver of the normal adult dog is capable of restoration of more than 100 per cent of its weight. During this process no signs of hepatic deficiency are observed except a transient upset of a few days' duration which probably is due to injury of the remaining hepatic tissue rather than to actual deficiency because of removal of tissue.

It is possible to prevent this restoration of liver following partial removal, and each of the three methods I will describe have their counterpart in most cases of chronic disease of the liver. Restoration of hepatic tissue is greatly reduced or completely absent in the presence of obstructive jaundice¹³, in the presence of marked cirrhotic changes in the liver, or when the portal blood supply to the liver has been reduced, as by an Eck fistula¹⁰. When one of these three conditions is present,

partial hepatectomy may be performed without subsequent increase in the size of the remaining part of the liver. With these methods animals may be maintained by proper dietary precautions with less than twenty per cent of the normal amount of hepatic tissue. These animals show surprisingly little evidence of decreased hepatic efficiency by any of the functional tests which we have employed. It is obvious that less than twenty per cent of the liver can accomplish the work of the entire organ.

Animals with complete obstructive jaundice caused by ligation of the common bile duct show many signs which are familiar to the physician. For the first few days the liver is enlarged, but it soon becomes smaller than normal, and there is rather extensive atrophy of hepatic cells. Under ordinary conditions the jaundiced dog does well for a few weeks, but after this time many interesting phenomena may appear. In the first place, a diet rich in carbohydrate becomes increasingly more necessary for the maintenance of these animals; we use milk, bread, and syrup. After two or three months a diet exclusively of meat, if taken, will prove fatal within about one week, but with a diet high in carbohydrates life may be prolonged for at least a year. Abdominal and esophageal varices develop and hemorrhage into the gastro-intestinal tract is of frequent occurrence. Duodenal ulcer³ occurs in an extremely high percentage of cases. Ascites develops spontaneously in the later periods of obstructive jaundice, and may be produced and relieved experimentally at an earlier period by dietary measures

Infectious cirrhosis, experimentally produced, is very similar to that rather infrequent type as seen in man. Following experimental cholecystenterostomy¹ there is an ascending infection of low grade involving the biliary ducts. After several months the gross appearance of the liver is not unlike that in the usual type of nodular cirrhosis, and on the cut surface of the liver are seen marked thickening and dilatation of the bile ducts, with marked cicatricial changes. Microscopic examination discloses that the infective process has encroached on the hepatic parenchyma and there is infiltration with leukocytes, and later, with round cells. There are definite zones of fibrous tissue surrounding the biliary ducts and in this there are many proliferating small bile ducts which present a picture suggestive of canalization such as that which occurs in a thrombosed blood vessel. Animals with infectious cirrhosis have no definite symptoms until the liver is extensively involved. Gastro-intestinal upsets, diarrhea, vomiting, and occasional melena, are usually the first symptoms noticed. With progression and continued attacks of gastro-intestinal bleeding, definite anemia usually develops, and a small amount of ascitic fluid may be present before death. Jaundice has not been observed, except as a terminal event.

To produce an experimental picture similar to the usual type of portal cirrhosis, it is necessary repeatedly to administer sublethal doses of a toxic agent which produces acute necrosis of the liver. We have used carbon tetrachloride and tetrachlorethane. The latter was extensively used as a solvent

for waterproof aeroplane paint before it was discovered that many workers with this poison contracted subacute yellow atrophy or cirrhosis. The method of administration to experimental animals determines somewhat the character of the lesions produced. If the material is injected into the spleen repeatedly, extensive atrophy of the left side of the liver occurs, and there is marked hypertrophy of the right lobes of the liver. Injection of the material by peripheral vein or subcutaneously, and also oral administration, is followed by more or less diffuse acute necrosis, with subsequent permanent changes in the liver. These changes also represent atrophy and hypertrophy but are found in close proximity in all portions of the liver. Consequently hypertrophic or atrophic cirrhosis may be produced, depending on the predominance of hypertrophy or atrophy. With increasing injury to the liver, these animals have most of the symptoms characteristic of portal cirrhosis. Gastro-intestinal upsets, diarrhea, and intestinal hemorrhage are usually the first symptoms observed, and definite retention of dye may be detected. With continuation of administration of the toxic agent, slight jaundice may be produced, and finally marked ascites may develop. Few of these animals die of actual hepatic insufficiency; many have died following excision of a small piece of liver for histologic examination, a procedure that is relatively harmless to the normal animal. Many die following extensive gastro-intestinal hemorrhage, and in many, chronic or subacute duodenal ulcer develops, with subsequent perforation and peritonitis. We have lost a large

number of animals following repetition of administration of the toxic agent. The necrosis produced seems to be more extensive as the liver becomes more severely injured, and a picture similar to that of subacute yellow atrophy frequently results. It should be noted that repetition of administration of the toxic agent is necessary, since this type of lesion is not progressive, and the animals improve considerably when the toxic agent is removed.

The chronic lesions of the liver we have been able to produce depend on the acute lesions repeatedly produced. Changes are not observed with frequent doses which are so small that acute necrosis is not produced. If doses that are too large are used, extensive necrosis results, from which the animal does not recover. The extent of acute hepatic injury obviously depends on the amount, toxicity, and specificity of the toxic agent used. In this respect it may be noted that we have been unable to produce hepatic necrosis with alcohol alone, but the addition of alcohol to several toxic substances produced much more extensive lesions. This increased toxicity may be due to the fact that most of these toxins are soluble in alcohol and that the effective dose is greatly increased when they are absorbed with the alcohol. Additional reasons for increased necrosis may be found in the fact that alcohol injures the liver so that it is unable to combat additional poisons. There is considerable evidence that the extent of hepatic injury also depends on variations in the more or less specific resistance of the liver to injury. In dogs much more exten-

sive lesions are produced by chloroform¹⁸ or carbon tetrachloride⁵ when the animals are maintained on a meat diet than if they are maintained on a diet high in carbohydrate and rich in calcium. The difference in activity of the hepatic cell appears to be correlated with the amount of glycogen in the liver and is less when the fat is more predominant. In this respect it should be noted that there is a cycle¹⁹ of changes in the glycogen and fat content of the liver, daily, with relation to the time of meals. Toxic agents are much more effective when administered to the fasting animal than when administered even several hours after the taking of food. Impairment of circulation in the liver increases the effectiveness of many hepatic poisons. After exclusion of the portal blood from the liver by an Eck fistula, carbon tetrachloride is more than ten times as effective as similar doses given to normal animals.

Many animals with considerable necrosis and with fatty changes in the liver show no symptoms, but when necrosis is more extensive, gastro-intestinal upsets, jaundice, and a small amount of peritoneal fluid may be noted. If further toxin is not administered, and if the necrosis is not too extensive, reparative processes begin in a short time. Within twenty-four hours there is marked leukocytic infiltration, and lymphocytes predominate later. The disintegrated hepatic cells appear to be removed by phagocytes, and their place is taken by new hepatic cells which have arisen by division of the adjacent uninjured hepatic cells. There is also a proliferation of fibrous tissue, apparently arising from that around the

portal spaces. Repetition of this process may give rise to extensive scarring of the liver, such as is seen in typical portal cirrhosis. Hypertrophic nodules develop, apparently by division of a few hepatic cells into many cells in a restricted area, so that lobular arrangement is not possible, and these islands of hepatic cells show little relationship to the blood vessels and biliary ducts of the liver.

In general, it may be said that the reparative processes of the liver tend to restore that organ to normal appearance, and it is surprising to see that after extensive injury, restoration of the liver may be so effective that the organ appears quite normal. Continual repetition of the process, however, gives rise to cirrhosis in which the size of the liver depends on the predominance of hypertrophy of the hepatic cells, or their absence due to the extensive cicatricial changes.

Our observations on experimental animals may be summarized best by considering those processes which in general appear to affect the response of the animal to the alterations in pathologic changes in the liver. One of the most striking observations, already referred to, is that the liver possesses huge reserve as evidenced by the extreme amount of liver that may be injured or removed without the production of any symptoms referable to the liver. Actual removal of as much as eighty per cent of that organ is not attended by a measurable loss of hepatic function, and sufficient liver remains to enable the animal to carry out all of its normal life and to appear to be well. In addition to the fact that less than twenty per cent of the normal

liver is necessary, the liver is capable of more than 100 per cent replacement due to the restoration of tissue. These observations appear to offer a definite explanation for the fact that the classical signs and symptoms of cirrhosis do not appear until the liver has been almost completely worn out by the repeated attacks of some toxic agent. It is to be noted, also, that the three factors which prevent restoration and repair of the liver in the experimental animal are each present in cirrhosis, that is, more or less extensive cicatrization of the liver, reduction of the actual blood supply to the liver, and jaundice. That cirrhosis is not entirely a hopeless condition, however, appears from the observation that animals with extensive cirrhosis, ascites, and jaundice do not continue to progress downward, but recover from their symptoms when the toxic agent is removed and a diet high in carbohydrate is administered.

The development of collateral circulation in the experimental animal appears similar to that found in the human being. In extensive cirrhosis from toxic agents, obstructive jaundice of long duration, or uncompensated extensive removal of hepatic tissue, the veins of the entire portal region are found to be dilated, and varicosities develop in the esophageal veins and in the abdominal wall. Hemorrhage into the gastro-intestinal tract is of frequent occurrence, but massive fatal hemorrhage is less common. Most animals with extensively injured livers have tarry or bloody stools and definite anemia. This intestinal bleeding is seldom continuous; usually it occurs in attacks lasting from two to ten days,

after which there are spontaneous remissions of short duration. In some animals a subacute or chronic duodenal ulcer develops from which hemorrhage may occur. Studies of the blood of these animals fail to show any definite alterations in the known factors concerned in coagulation. It is obvious that the control of coagulation is less stable than normal when the liver is extensively injured. Values for blood fibrinogen and blood platelets may at times be found to be low, but later, in the same animal, may be normal. Coagulation time and clot retraction time are likewise variably found to be delayed or normal. Obviously, other factors affect the coagulation of the blood in addition to the definite, although vague, influences of the liver. That the hepatic factor, however, plays a definite part in the hemorrhages, is evidenced by the fact that we have never observed this type of bleeding in dogs prepared for removal of the liver in three stages. In this method both the vena cava and the portal vein are occluded below their entrance into the liver and there is extensive collateral circulation sufficient to return both caval and portal blood to the heart; the liver is only slightly injured, if at all, and bleeding or a change in the factors of coagulation does not occur. Recovery of animals from extensive hepatic injury is accompanied by recovery from this hemorrhagic tendency, although the collateral circulation may not appear to be altered.

Since a small amount of hepatic tissue is sufficient to maintain the normal functions, both metabolic and excretory, of that organ, it does not appear surprising that most functional

tests fail to indicate hepatic pathologic changes until they are extensive. Many of the metabolic tests which have been devised are influenced by the previous diet and the condition of the other organs of the body, as well as by the condition of the liver. This is particularly true of a number of tests devised to determine the activity of the liver in carbohydrate metabolism, and some of these we have found to give similar results when applied to a normal animal as to one completely deprived of its liver. Tests based on the activity of the liver in the metabolism of protein give the anticipated results in entire absence of the liver but deviation from normal is not appreciable in cases of hepatic injury unless the injury is extreme. In most of our experiments on rapidly failing animals failure of protein metabolism was present, and usually the fatal termination ensued in a few days. Quantitative estimation of the detoxicating power of the liver, particularly with salicylates, camphor, compounds of phenol, and so forth, have not been satisfactory in our hands. We have distinct evidence that many of these compounds are conjugated partially or completely in the entire absence of the liver. The guanidine¹⁷ content of the blood may be definitely elevated in the presence of acute intoxication with extensive hepatic necrosis, but it rapidly returns to normal without giving any indication of the amount of permanent injury to the liver.

Tests designed to evaluate the excretory function of the liver appear to be the most satisfactory of any hepatic tests we have used. Failure of this function is indicated by bilirubinemia:

this is not observed in the experimental animal without biliary obstruction unless extensive hepatic injury is present. Acute hepatic necrosis is usually accompanied by bilirubinemia of a degree approximately parallel to the extent of the hepatic injury. In acute and chronic hepatic injury, the van den Bergh reaction is direct. Extensive lesions of the liver also produce definite delay in the excretion of bilirubin and other chromogenic substances which may be injected intravenously. We have recently determined the retention of bromsulphthalein in a series of dogs with varying degrees of experimentally produced cirrhosis. Several tests were made prior to surgical exploration and biopsy, and several tests were made after this procedure, before additional carbon tetrachloride had been administered to produce more extensive cirrhosis. In each animal the degree of retention of dye was compared with the gross and microscopic appearance of the liver. For the most part, there was very satisfactory correlation between the degree of injury to the liver, as estimated from the gross appearance and histologic section, and the degree of retention of dye. There were, however, exceptions in sufficient numbers to demonstrate clearly that the last word is yet to be said regarding the function of the liver and its pathology. A few animals with extensive cirrhotic changes, usually hypertrophic, gave no evidence of retention of dye, although few normal-appearing hepatic cells could be demonstrated histologically. A few normal animals, with no demonstrable hepatic lesions, gross or microscopic, showed marked retention

of dye. It should also be mentioned that a few livers, which microscopically appeared to be definitely cirrhotic, appeared grossly to be normal.

Ascites develops spontaneously in animals with very extensive cirrhosis, and also following obstructive jaundice of long duration. Under both of these conditions we have been able to produce and remove ascitic fluid by dietary measures. Animals with obstructive jaundice were maintained for three or four months on a diet of milk, bread, and syrup and showed no evidence of ascites. They were then fed meat for three or four days. In most animals the presence of ascites could be determined by inspection of the abdomen within twenty-four hours after the feeding of meat was instituted. It was not uncommon for the abdominal circumference of an animal weighing five to seven kilograms to increase from an original measurement of about 35 centimeters to more than 50 centimeters, and from one to three liters of fluid could be aspirated from the peritoneal cavity. In many animals this process was repeated several times. Certain animals appeared more resistant than others, but in all ascites developed within four days of the initiation of repeated feeding of meat. In a few experiments the animals refused to eat meat in any form, and feeding by stomach tube was not very successful. Most of the animals that were refractory to formation of ascitic fluid became less so as the interval following complete biliary obstruction increased, and with repetition of the regimen of meat feeding. As the process was repeated more and more, ascitic fluid could be formed with smal-

ler and smaller intake of meat. Experimental cirrhosis must be very extensive before ascites can be produced in this way, but if the cirrhosis is extensive enough feeding of meat will produce ascites.

The active substance which produces ascites in these animals is probably not

liters of newly formed ascitic fluid can be withdrawn. Control experiments with the addition of salt to the diet have produced entirely negative results.

The ascites disappeared in most instances when the meat or the meat extract was withdrawn from the diet.



FIG. 1. Atrophy and hypertrophy of the liver. In the upper row are the lobes of a dog's liver three years and three months after a series of injections, lasting three months, of small amounts of carbon tetrachloride into the spleen. In the lower row are the lobes of a normal liver of the same weight removed from a normal dog of the same size. Hypertrophy of the right lateral lobe and atrophy of the other lobes may be noted. This condition is not changed from that seen at exploration two and a half years previously.

protein. Proteins of milk do not favor the production of ascites. The active principle appears to be in the water-soluble extractives of meat. The feeding of meat extract which is free from protein and fat produces results which are even more striking than the feeding of meat. Within four to six hours after feeding twenty-five grams of meat extract to animals with obstructive jaundice of long duration, or with extensive cirrhosis, marked abdominal distention is evident and two or three

The substitution of large amounts of carbohydrate to the diet seemed to aid in the removal of the fluid; the fluid disappeared more rapidly than when all food was withheld. With repetition of the formation and removal of ascitic fluid, the animals became more susceptible to accumulation of fluid, and the time of disappearance of the fluid with the feeding of glucose became greater and greater. The mercurial diuretics, given in small doses, were also effective in reducing the as-

cites, but these too became less effective after several administrations. Transfusion of blood into those animals with ascites that showed definite evidence of anemia, and in some instances, also, definite reduction of the values for plasma protein, were effective in removal of ascitic fluid. Transfusion was not effective in the animals with ascites if these changes in the blood were not present. In all of our experiments the progressive loss of resistance to the accumulation of ascitic fluid was accompanied by increased in-

jury to the liver, either by the increasing duration of biliary obstruction or by continuation of administration of carbon tetrachloride.

The mechanism by which meat extract produces ascites in these animals is not understood. In the animals in which it does produce ascites there does not seem to be any alteration in the control of peritoneal fluids prior to the administration of the extract. If saline solution or ascitic fluid, either from dogs or men, is injected into the peritoneal cavity of dogs, it is absorbed



FIG. 2. Experimental cirrhosis from carbon tetrachloride. The liver of a dog which had received 100 doses (5 c.c. each) of carbon tetrachloride over a period of two years.

as rapidly by animals which are in the pre-ascitic stage as by normal animals. It would appear that meat extract might produce ascites by one of three possible mechanisms, none of which is proved: (1) because of a specific colloidal effect on the blood or vessels, which enables water to diffuse into body cavities more readily than

normally; (2) a specific effect on the liver, which produces constriction of the intrahepatic portion of the portal system with subsequent sufficient increase in portal pressure to produce vascular changes in the abdominal viscera, or (3) specific irritation of the peritoneal surfaces, which increases the secretion of fluid from these surfaces

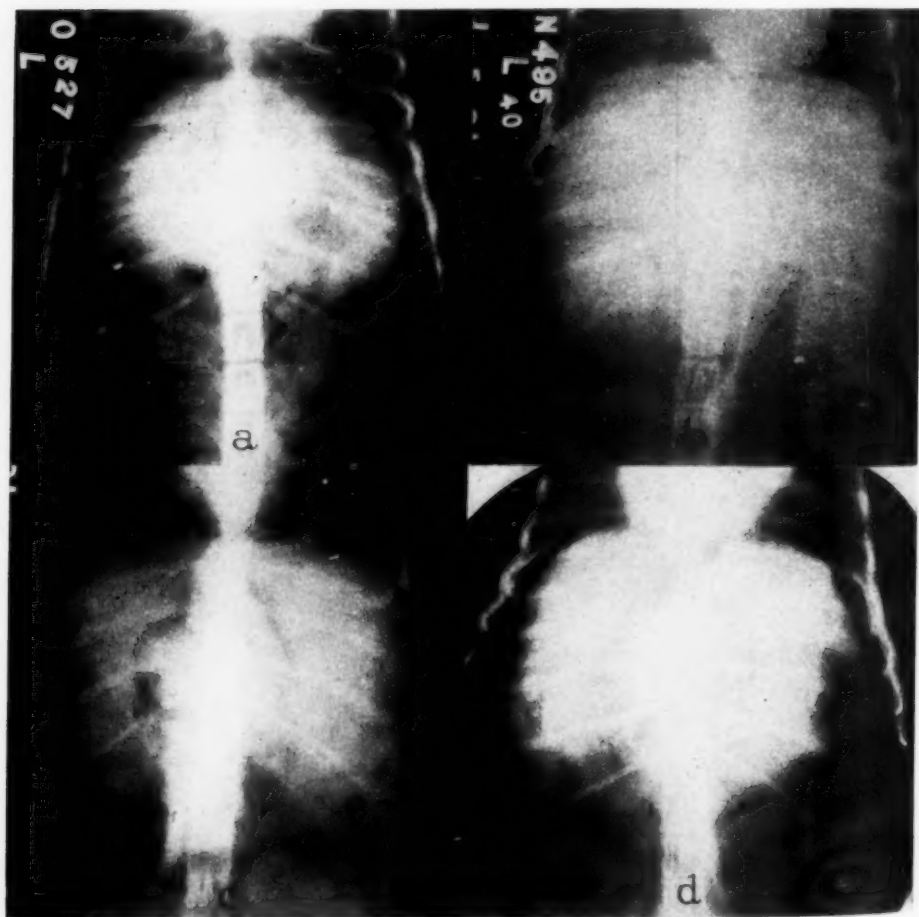


FIG. 3. Hypertrophic cirrhosis with subsequent atrophy. Size of the liver of dogs with pneumoperitoneum; *a*, normal animal of the same weight and size as that illustrated in *b*, *c*, and *d*; *b*, marked hypertrophy which occurred in one year in which the animal received 150 doses (1 c.c. each) of tetrachlorethane; *c*, same animal as that shown in *b* sixteen days later; *d*, same animal as that shown in *b* and *c* after twenty-eight more days. Additional tetrachlorethane was not given and within three months the liver had returned to normal size.

and inhibits their absorption of fluid. It is to be noted that in any case, extensive injury to the liver must be present, so that it appears obvious that a normal liver must compensate for, or detoxify, this active agent which will produce ascites when the liver is extensively injured.

In all of our experimental work, the proportion of carbohydrate in the diet of animals with extensive hepatic lesions is of outstanding importance. In the entire absence of the liver, animals succumb to hypoglycemia unless glucose is given. We have maintained dogs with complete biliary obstruction for six to twelve months on a diet of milk, bread, and syrup, and have repeatedly observed the rapidly fatal effects of diets composed entirely of meat. After biliary obstruction has been present for three months we have

been unable to cause a dog to survive on a diet entirely of meat for more than six days. The protective value of carbohydrates against hepatic injury from toxic agents is well illustrated by the following experiment.

Four dogs were maintained on a diet of milk, bread, and syrup, and four on a mixed diet, containing about 25 per cent meat protein, 50 per cent carbohydrate, and 25 per cent fat; four other dogs received as much meat as they desired. All of these animals received daily doses of 10 c.c. of carbon tetrachloride by mouth. At the end of one month, one of the animals that was fed meat had marked ascites and died two weeks later. Within three months ascites developed in one of the remaining animals, which later died, and the other two meat-fed animals were distended with ascitic fluid. In the same period of three months, the other eight dogs remained in good condition and showed no signs of ascites. Biopsy revealed that the livers of the animals to which meat had been fed suffered more extensive injury than was

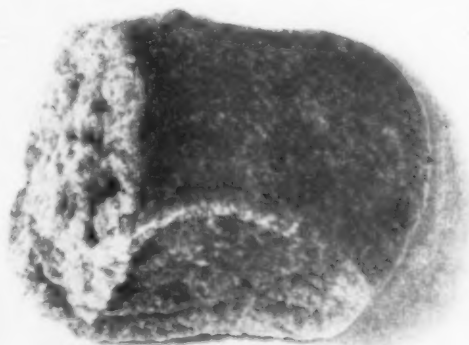


FIG. 4. Hypertrophic cirrhosis; specimen removed from dog the day the roentgenogram shown in figure 3 b was taken.

present in the other animals, although lesions with the definite appearance of cirrhosis were present in all.

Glucose is of definite value following surgical procedures on animals with extensively injured livers. Following operation, these animals are markedly lacking in resistance, and extensive degenerative changes rapidly occur in the injured liver. Intravenous injection of large amounts of glucose appears to enable many animals to recover that would almost certainly succumb had the glucose not been given. This same specificity for glucose appears in animals suffering from acute intoxication following excessive administration of hepatic toxins.

SUMMARY

From our experimental studies of animals with definite pathologic lesions of the liver we feel justified in drawing a few general conclusions:

First, because of the extensive reserve and extensive reparative processes of the liver, symptoms of chronic hepatic disease appear as evidence that most of that organ has been destroyed and that the capacity for reparative processes is almost exhausted. In our experiments, however, removal of the agent responsible for the production of hepatic lesions has enabled the animal (and liver) to recover sufficiently to maintain fairly normal life.

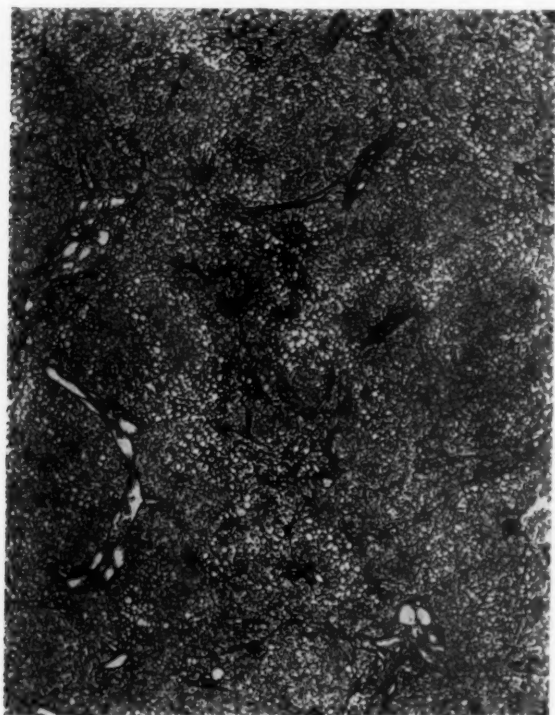


FIG. 5. Loss of lobular arrangement of the liver and increased connective tissue. Section of specimen shown in figure 4 ($\times 50$).

Second, a definite tendency toward intestinal hemorrhage is present in animals with extensively injured livers, and this tendency improves as the condition of the liver is allowed to improve, although the distended varices of the collateral circulation remain.

Third, ascites in the experimental animal may be controlled by dietary measures.

Fourth, diets rich in carbohydrates appear to be essential for the maintenance of animals with extensively injured livers.

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Further Studies in Allergic Migraine:

Based On a Series of Two Hundred and Two Consecutive Cases*†

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IN a recent work on the hereditary factor in allergic diseases by one of us¹, it appears that migraine is interchangeable in the linkage with asthma and seasonal hay fever, which is excellent evidence that they have a common etiologic factor, namely, a specific sensitization. That protein sensitization is the causative factor in true bronchial asthma and seasonal hay fever is generally accepted. In a previous study² of allergic migraine a family history of allergy was elicited in 85.4 per cent of all cases. We observed that many asthmatic patients also suffered from migraine. A large per cent of migraine cases studied gave definite reactions to one or more foods and the results of treatment, based on our allergic findings, were equal to those obtained in the treatment of asthma. Our study led us to believe that the exciting factor in probably 100 per cent of true migraine cases is a specific sensitization to one or more foreign proteins.

The data contained in this paper were collected from a review of 202

consecutive cases of migraine examined at our private clinic, of which there were 135 female and 67 males; and from a careful questioning of 198 practicing physicians, 260 medical students, 107 nurses, 845 women teachers, 581 male and 521 female high school students, and 270 unemployed.

We were stimulated to give this subsequent review as we believe we have much additional evidence to substantiate the conclusions drawn from our first study.

AGE AT ONSET

Alger³ finds 3 per cent of migraine cases develop before 10 years of age. Block⁴ states that the vast majority of cases develop symptoms before 25 years of age. Flatau⁵, in a history of 500 cases, shows that in 12 per cent the trouble started before the age of 15. Timme⁶ remarks that adolescence is the chief time of onset. Of our series of 202 cases, 60, or 29.7 per cent, gave a definite history of onset of symptoms before they were 10 years of age. An additional 30.6 per cent manifested symptoms before 20. The fact that 60.3 per cent of all migraine develops before 20 is significant, if our theory as to etiology, which will be discussed later, is correct.

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†From the University of Oklahoma Medical School and the Balyeat Hay Fever and Asthma Clinic, Oklahoma City, Okla.

TABLE I

Distribution of age at onset of clinical manifestation of migraine in patients of all ages, based on 202 cases.

Age at Onset	No. of Cases	Per Cent
First decade	60	29.7
Second decade	62	30.6
Third decade	50	24.7
Fourth decade	25	12.3
Fifth decade	3	1.4
After fifth decade	2	.9

In ascertaining the history of onset of migraine from adults many will answer the question as follows: "As long as I can remember", or "About the time I started to school, as I remember the teacher would send me home from school on account of my headaches and vomiting". We are caring at present for a number of cases of migraine under 5 years of age, most of whom came not on account of the headaches but for relief of some other allergic syndrome. We have a few cases whose symptoms did not appear until after 40. Organic brain lesion, however, should always be thought of in one developing headache at this age.

INCIDENCE OF MIGRAINE

No reference has been found in the literature to the frequency with which this symptom complex occurs. Business men, society women and students are reported to be more subject to the syndrome than other people. That migraine is more common in women

than men is frequently mentioned. As a means of trying to determine the number of people who suffer with typical attacks of migraine, we interviewed personally, or (with the assistance of Dr. H. H. Cloudman, chief physician to the Oklahoma City Public Schools, through a detailed questionnaire) obtained data concerning the history of migraine in 2,728 individuals.

It appears from the above findings that migraine is about twice as common in the female as in the male, and that it occurs twice as often in doctors and male high school students as in unemployed male laborers. We have always contended that migraine, like other allergic diseases, occurs in those with a highly developed vegetative nervous system, therefore the percentage in the unemployed laborer should be much less, and according to our findings it is. Considering the fact that the incidence of migraine is nearly 4 per cent in the indigent male labor-

TABLE II

Incidence of migraine in different classes of people.

	Total No.	No. with Migraine	Per Cent
Physicians and medical students	404	31	7.9
Nurses	107	13	12.1
Unemployed male laborers	270	10	3.7
Women teachers	845	88	10.4
High school students, male	581	39	6.7
High school students, female	521	71	13.5

er, and about 10 per cent in the student and business class, a conservative estimate would place the percentage in people at large at about 7 per cent. Considering the age of onset and the disappearance of symptoms we estimate the number of people in the United States who now suffer from the syndrome at approximately 4,000,000.

From table II it can easily be seen that migraine is more common in business men, professional men, and teachers, than in other people. For example, we found that 7.9 per cent of all physicians and medical students gave a history of typical migraine; 10.4 per cent of all women teachers suffer from the disease; while less than 4 per cent of the indigent laboring men suffer from the symptom complex.

An answer to the question as to why migraine is more common among business men, professional men, and teachers, than in farmers, factory workers, and the indigent laboring class, is not easy. We wish to offer the following explanation as a possible answer. In a study of 1,217 patients with asthma and hay fever one of us¹ showed that the general health of allergic patients is far above the normal, and in the study of the mental activity of allergic children, we⁷ found 75 per cent were either in the superior, very superior, or genius class, which is far above the average. From our study of those who suffer from migraine it appears that they follow the rule of other allergic patients in regard to general health and also mental activity. One who has the ability to become specifically sensitive and suffer from some allergic condition has a highly developed vegetative nervous system.

Such a system is a prerequisite for a good business man, professional man, teacher, etc. The boy on the farm, or the one who comes from the laboring class, who inherits a highly developed vegetative nervous system, soon learns that he is a good student and enjoys his school work. He then becomes a university student. Therefore, from these children come our professors, doctors, lawyers, preachers, bankers, society women, etc. In other words, they naturally drift into the part of society where they belong.

SYMPTOMATOLOGY

Not unlike asthma, the frequency of migraine headache varies greatly. Some patients suffer once a week, others every two or three weeks or every two or three months. The average frequency in our series is one attack in three weeks. Some patients are never entirely free from a slight headache between attacks. The duration of the attack again varies greatly, ranging from 12 to 96 hours. The average duration in our cases was 30 hours. In some instances a remarkable periodicity is noticed, especially in women who have attacks just before or during the menses. Again, like asthma, migraine may disappear during pregnancy.

Typical attacks of migraine consist of: *First*, a prodromal stage; *second*, aura; *third*, attack; *fourth*, post-migrainous symptoms.

The *prodromal stage* in our series was characterized by a period of depression with nervousness and irritability in 26 per cent; 19 per cent stated that they felt unusually well the day previous to the attack; bulimia was

noted in 23 per cent; and 53 per cent gave a history of a druggy or profound sleep the night preceding the headache.

The *aura* was manifested by faintness or vertigo in 21 per cent; scintillating scotomata in 81 per cent; hemianopsia in 22 per cent; and photophobia in 38 per cent. Auditory and olfactory symptoms were complained of by 4 per cent and 3 per cent respectively. Paresthesia of the hands occurred in 81 per cent; of the feet in 37 per cent; and of the face in 18 per cent. Motor symptoms were manifested by motor aphasia in 44 per cent; paresis in 0.6 per cent. Vasomotor disturbances were complained of in 7 per cent and mental confusion was reported or observed in 31 per cent.

The *attack* consisted of hemicrania at one time or another in 94 per cent of all cases studied, while the remaining 6 per cent never experienced pure hemicrania. A unilateral headache which became generalized was noted in 49 per cent. Nausea occurred in 73 per cent; emesis in 65 per cent. Pyrexia has been observed in some of the children during an attack.

Post-migrainous symptoms consisted of exhaustion in 40 per cent of our cases; polyuria in 6 per cent; rhinorrhea in 9 per cent; and a tendency toward sleepiness in 18 per cent.

We have observed a change from the typical migraine attack in a number of patients in the late 30's and early 40's. The headache became chronic, less severe, and usually generalized. The symptoms of the aural stage are usually less marked, nausea persists, but emesis is rare.

In children the headache may be very severe but is usually milder than

in adults. Gastric symptoms are much more common and severe in children than in adults. The so-called cyclic vomiting in children is probably migraine. Like asthma and other allergic symptom complexes, one may live under exactly the same environment, on a routine diet, and yet for some reason either lose his attacks entirely or have them milder for a period of years, only again to resume them in their original severity. Migraine frequently disappears in the late 40's in both men and women, but many continue to suffer throughout the 50's and early 60's.

THE HEREDITARY FACTOR IN MIGRAINE

That heredity is the most potent factor in the production of migraine is not questioned. Timme⁸ states that 50 per cent show this characteristic and that the mother transmits the disturbance in 75 per cent of the cases. Hassin⁹ says "heredity is most important in considering the cause of migraine. It may be direct (migraine in parents) or indirect (various other nervous or mental disorders in the family)." Both Timme and Hassin are neurologists and have studied the subject from a neurological standpoint. Neither mentions the possibility of a specific sensitization as an etiologic factor, or the relation that exists between migraine and the well established allergic syndromes. In studying many of the family trees in our series we have been impressed with the fact that the disease is interchangeable in the linkage with the well established allergic syndromes; namely, asthma, seasonal hay fever, perennial hay fever, urticaria.

and certain forms of eczema and colitis. It appears that it is only one of a number of syndromes which are metamorphosed in passing from parent to offspring. For example, five children in one family might be specifically sensitive to wheat. From such a sensitivity asthmatic symptoms might appear in the first child, eczema in the second, hay fever in the third, urticaria in the fourth, and migraine in the fifth. The mother of these five children might have been a hay fever sufferer due to the Russian thistle pollen and her mother have had asthma due entirely to a specific sensitivity to cat hair. The specific state is not inherited, but only the ability to become sensitive.

Four family trees are being offered to show the relation between migraine and the other allergic syndromes. In the pedigree shown in chart 1 you will note that the patient suffers from migraine and urticaria, that the father of this patient also suffered from migraine, but his sister had asthma, and the paternal grandmother had asthma, one of her sisters had asthma, and one brother suffered from asthma, but there is no record of migraine in her immediate family. The patient's son is also an asthmatic. In other words, in one generation asthma appears; in the next generation some of the children have asthma, others migraine; in the third generation migraine and urticaria; in the fourth, migraine only.

The family tree as shown in chart 2 is of interest as we find a patient with migraine, who has one brother and one sister with migraine, and whose mother had migraine. He has one son with hay fever and asthma. This son

has a newborn son. In all probability this newborn will not develop migraine, hay fever or asthma, but may develop a sensitivity to food and have eczema, urticaria or colitis.

In chart 3 we find a patient who suffers from epilepsy of a type that is definitely sensitive to food and has been controlled by food elimination. She has one sister with asthma and one with epilepsy. The sister with epilepsy has not been treated, but she has a child who has asthma. Our patient's grandmother had migraine, one maternal aunt had migraine, and one asthma. Her great grandmother had migraine and her great grandmother's sister had asthma. Here we find migraine transmitting epilepsy and in turn epilepsy transmitting asthma. Some of the neurologists have tried to show us that migraine is very closely associated with epilepsy. We have not found it so. We believe that those epileptics whose family history is saturated with migraine should be thoroughly studied from the standpoint of food sensitivity as a cause of their epilepsy.

Our patient as shown in chart 4 has migraine, asthma and eczema, and this is not an uncommon finding. He has a sister with asthma, his father had migraine, one paternal aunt with urticaria, one with migraine, and his paternal grandfather had asthma. The paternal grandmother had migraine and eczema. More than three-fourths of all migraine cases that we have studied suffer from other allergic diseases.

From the four cases presented and many similar ones we have studied, it appears that migraine is interchangeable in the linkage with asthma, hay

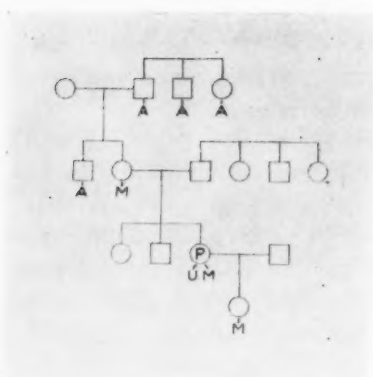


CHART 1. Showing the relationship between asthma and migraine.

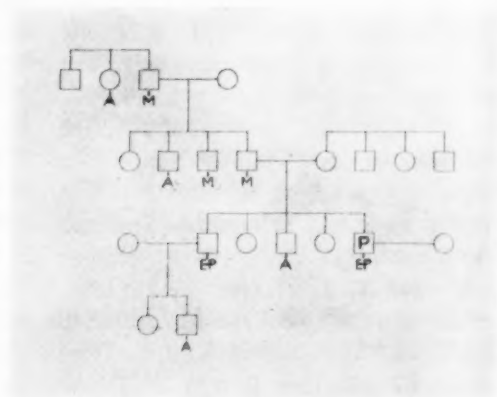


CHART 3. Showing the relationship between certain types of epilepsy and migraine.

KEY TO CHARTS

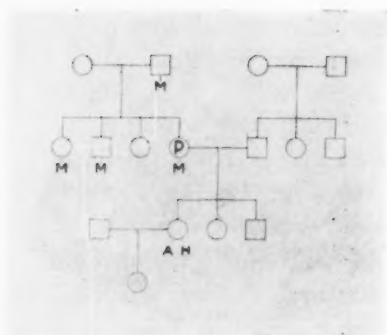
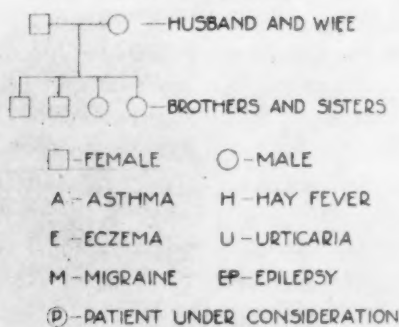


CHART 2. Showing the relationship between migraine and hay fever.

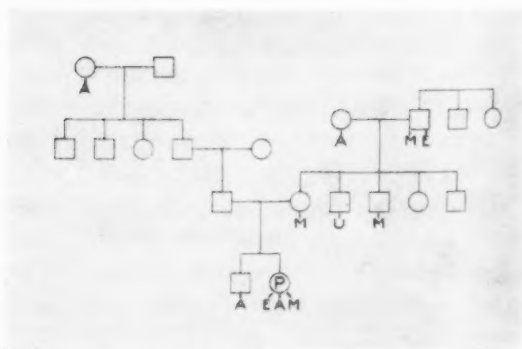


CHART 4. Showing that migraine cases frequently have other manifestations of allergy.

fever, urticaria, and certain types of eczema, colitis and epilepsy. This observation, along with the clinical findings that 81.1 per cent of all of our cases suffer from other allergic syndromes is excellent evidence that the etiology is the same, namely, a specific sensitization to foreign protein.

Our parents and we inherit from the same germ plasm and therefore the same plans and specifications are used in our make up, which accounts for our having traits in common. We inherit only a hypersensitive cellular make up.

In some cases there seems to be a definite tendency to become sensitive to certain atopic groups, as has been pointed out by Coca⁸. Some patients apparently become sensitive to atopic substances in food with ease compared to other groups. Others develop a sensitivity to pollen with similar ease, others to animal dander, etc. The fact that a fair number of eczema, urticaria and migraine patients are comparatively negative to the inhalant group of atopic substances, both by testing and clinically, is striking. In other words, it appears that some patients may become allergic to one or more foods early in life and have eczema, urticaria or migraine, but never become sensitive, or if so to a sufficient degree, to the inhalant groups, in spite of the degree of contact, to develop asthma or hay fever. One of us⁹ has pointed out the fact that the massiveness of the contact dose has much to do with determining the atopic substance to which the patient will become sensitive.

We have also shown¹⁰ that a food sensitivity usually manifests itself in

the form of eczema, asthma or perennial hay fever rather early in life. We naturally would therefore expect migraine, if the etiology be that of a food sensitivity, likewise to appear at an early age, and from our findings it actually does.

In this series of cases a positive familial history of migraine or a family history of the well accepted allergic diseases, was elicited in 167, or 82.1 per cent. There were 145, or 71.3 per cent, with a unilateral family history, and 23, or 11.4 per cent, with allergic histories on both sides of the family. Of those with a unilateral family history the trait was transmitted through the mother in 112, or 55.4 per cent, and through the father in 57, or 28.2 per cent, of the cases. The figures relative to the transmission of the disease through the female do not correspond to those frequently quoted. Spain and Cooke¹¹ found a positive antecedent history in 58.4 per cent of a series of 462 cases of bronchial asthma and hay fever studied. Rowe¹² reported the occurrence of allergy in the antecedents in a series of bronchial asthma, in 56.4 per cent. We¹³ reported a series of 1,000 cases of asthma and hay fever in which there was a positive antecedent history of allergy in 60.1 per cent; a series of 188 cases of urticaria with a family history of allergy in 67.6 per cent; and a series of 181 cases of eczema, in which a definite familial history of allergy was present in 64.3 per cent of the cases.

It appears from our findings previously given in this paper that an antecedent history of allergy is found in as great or a greater per cent of patients who suffer from migraine

than in those who suffer from asthma or hay fever. The fact that migraine is interchangeable in the linkage with asthma and hay fever and that there is a family history of allergy in as great or greater per cent of cases than in the well established syndromes leads us to believe that they have a common etiologic factor.

PREDISPOSING FACTORS

Like asthma, there are many conditions which play a part as predisposing factors. Consideration should be given the following:

- (1) Physical fatigue,
- (2) Mental fatigue and depressed states,
- (3) Thyroid dysfunction,
- (4) Genito-sexual,
- (5) Toxic states,
- (6) Disturbance of the special senses.

Typical attacks of migraine may follow exhaustive physical exertion, prolonged worry, extreme depression, or, in women, occur just previous to or at the menstrual period. Endogenous toxins, such as from infected teeth, tonsils, or toxins from an exogenous source, such as partially burned gas fumes, may bring on headache. Refractive errors, or a disturbance of the normal hearing, smelling, seeing or tasting, may play a part in precipitating an attack. The various factors just mentioned must be considered not as basic ones but predisposing only. In many of our cases after the food to which they were specifically sensitive was removed from the diet they remained free from their usual migrainous attacks in spite of the menstrual period, the physical fatigue, thyroid

dysfunction, toxic state, or disturbance of the special senses, as the case might be. We are inclined to believe that the stress and strain of life as a predisposing factor has been very much overestimated, since 29.7 per cent of our cases had typical migraine before 10 years of age and an additional 30.6 per cent before 20. In these cases the stress and strain of life surely had little to do with their symptoms.

ETIOLOGY

Over a century ago it was suggested by some French investigators that migraine, asthma, hay fever, eczema, urticaria, and epilepsy, might be of similar origin. In 1890 and again in 1900 Haig¹⁴ wrote rather extensively concerning migraine, in which he felt that an increase in uric acid was the chief cause. The disease received but little investigation until the last decade. Pagniez¹⁵ in 1920 treated the syndrome by the use of peptone on the assumption that it was anaphylactic in origin. Ball¹⁶ reported a series of 20 cases treated with peptone and states that clinically migraine is associated with asthma, hay fever, urticaria, epilepsy, and therefore he believes that it is due to a hypersensitiveness to food. In 1927 Vaughan¹⁷ studied 33 cases from an allergic standpoint. This seems to be the first series of migraine cases to be carefully tested for a food sensitivity and their treatment based on such findings. Vaughan was the first to show that patients sensitive to food or foods could be partially or wholly relieved by specific avoidance, and that an attack of headache could be produced by the ingestion of the specific food. Later in the same year Rowe¹⁸ mentions four patients with migraine

who obtained great relief on diets based on the elimination of the foods to which he found them sensitive. In 1928 Rowe¹⁹ states that food allergy must be considered a possible cause of all cases of migraine. In 1930 one of us² reported a series of 55 cases studied from the standpoint of protein sensitization. Treatment of these cases consisted of eliminative measures based on positive food findings. The cases were studied primarily for the purpose of determining the exciting factor or factors. It was concluded from this small series that the exciting factor in probably all cases is a specific sensitivity to one or more food proteins. Recently Eyermann²⁰ has reported a study of 63 cases in which he showed that many cases could be freed from their headaches by elimination of the foods to which they are sensitive, and their headaches could be produced by deliberate partaking of the specific food. Recently in reviewing the histories of 100 cases of asthma in the adult we found that 20, or 20 per cent, had associated with their asthma typical migraine. In other words, it appears that the symptom complex is more common in allergic than in nonallergic people. Beckman²¹ has suggested a disturbance of the acid-base balance as an etiologic factor in allergic diseases. R. and S. Weissmann-Netter²² found the hydrogen ion concentration and alkali reserve normal in the migraine patient in periods of freedom from attacks but a tendency for alkalosis to develop 48 hours prior to an attack. It is believed by many that carbohydrates have much to do with precipitating an attack. Zinsser²³ states that carbohydrates are non-antigenic sub-

stances; therefore they could not be the exciting factor but might act as a predisposing factor.

The present series of 202 cases under consideration includes the 55 previously reported. In our study of the last 147 cases the intradermal method of testing for food sensitivity has been employed much more extensively. In every case studied a reaction to one or more proteins was found. We use the scratch method of testing routinely but this is always followed routinely by the use of the intradermal method. It has been our experience that a large percentage of the foods do not react to the scratch test and the intradermal method therefore is necessary to find all food factors. If a question arose as to a reaction being of a nonspecific origin, passive transfer was employed. Of the cases studied, 70, or 34.2 per cent, suffered from asthma; 98, or 48.5 per cent, had hay fever; 41, or 20.3 per cent, had eczema; 35, or 17.3 per cent, had urticaria; and 14, or 6.9 per cent, had colitis. In the series we naturally found many sensitive to the inhalant group of atopic substances. During the last year all cases have been tested with allergens made in our own laboratories, which have been tested clinically for potency. Any food or any combination of foods, may cause migraine, but the following foods, as etiologic factors, are of importance in order as they are numbered:

- (1) Milk,
- (2) Wheat,
- (3) Eggs,
- (4) Nuts,
- (5) Beans,
- (6) Fish.

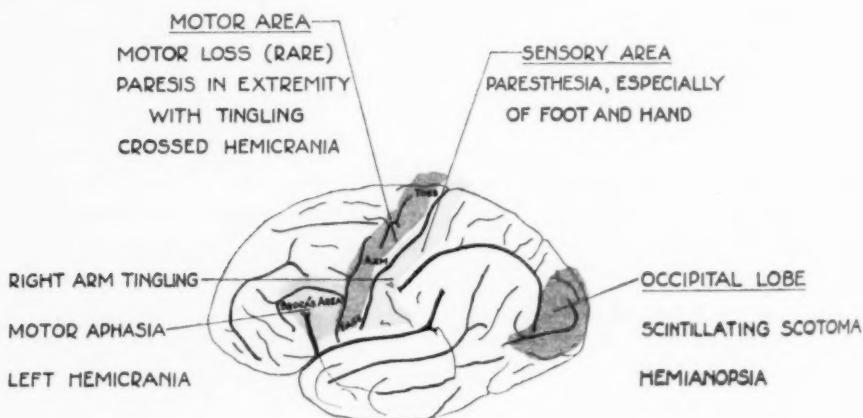
Multiple sensitization to food is very much the rule. Frequently, however, one food may be of primary importance clinically. We have learned that a one plus reaction to a particular food may be much more important than a four plus reaction to some other food.

PATHOLOGY

Little has been written on the pathology of migraine. Church and Peterson²⁴ remark, "In the absence of any known morbid changes we must fall back on theories and analogies."

An acceptable theory of migrainous pathology must take into consideration the frequency in early life, the influence of the vegetative nervous system, and the frequently recurring condition which leaves no permanent organic change that may be demonstrated in histologic study. Endarteritis is not an acceptable theory because approximately 60 per cent of the migraine patients will suffer before the second

decade. Further, the pathologic theory must explain the multiple cortical manifestations; namely, scintillating scotomata, hemianopsia, paresthesias, motor aphasia, paresis and occasionally auditory or olfactory aura. One patient presents the following symptoms in order named: paresthesia of the right finger, progressing up to the shoulder; then scintillating scotomata, followed by hemianopsia, motor aphasia, mental confusion, with the headache on the left side, and with subsequent nausea and vomiting. The headache may become generalized, or remain localized, or pass down into the upper cervical region. What is the most likely histopathogenesis of these symptoms? It seems somewhat improbable for this to be due to vasospasm. The isolated and definite areas affected do not correspond to the arterial supply of the cortex. Rackemann²⁵ states that the possibility of cerebral vascular spasm, as shown by Cobb and his associates,



CEREBRAL LOCALIZATION OF COMMON MIGRAINE SYMPTOMS

Multiple localized areas of vasomotor dilatation seem to explain best the symptoms of multiple localized cortical irritations complained of by those who suffer from migraine.

makes it proper to consider migraine on a pathological as well as on a clinical basis as related to other allergic manifestations. With the vasomotor spasm theory we cannot agree. We believe that there is ample evidence to classify migraine as allergic, and therefore we see no reason why one should consider the pathology of migraine as differing from the typical pathological lesion of other allergic diseases, namely, local edema. In urticaria we have a lesion characterized by primary dilatation of the blood vessels of the cutis, followed by an exudation of fluid into the tissues with cellular infiltration. Hansel²⁶ has described in detail the allergic reaction of the nasal mucosa. In all of these allergic manifestations there is a marked pathogenic similarity. In view of this fact, why should we consider that the allergic reaction within the cortex is different histopathologically from other allergic reactions? It is reasonable to assume that the attack is due to a sudden dilatation of the vessels of the cerebral cortex instead of a spasm. The fact that about 15 per cent of the patients can obtain freedom from their headaches by the use of epinephrin or ephedrine is evidence in favor of this theory. Until more convincing evidence is presented we see no reason to assume that the allergic pathogenesis differs in migraine from any of the other allergic diseases.

The question naturally arises as to why the local dilatation of the vessels of the cerebral cortex of the brain should occur, and not in other structures of the body. It appears that the French experimenter, Arthus²⁷, may have explained this phenomenon. He observed that the mechanism of

anaphylaxis, for example, in the rabbit differed from that of the guinea pig, but only in the site of the reaction. In the rabbit, the site of the occurrence of the reaction is in the muscle of the arteriole of the lung. The arterioles are constricted completely so no more blood can pass through. The blood pressure falls completely and the animal dies. In the guinea pig the site of the reaction is in the muscle of the bronchiole. In the dog the site of this reaction is in the liver. Thus, the site of the anaphylactic reaction due to the same foreign protein in one animal might be in the muscle of the bronchiole, in another in the muscle of the arteriole of the lung and in the third, in the liver. Anaphylactic and allergic reactions are not the same, but similar in many respects. Clinically, one patient may be sensitive to wheat and have asthma due entirely to the sensitization to that specific food; another have no symptoms of asthma whatsoever but have hives; the third patient manifest symptoms of perennial hay fever due to a wheat sensitivity, and the fourth patient local symptoms in the brain, namely, migraine, due entirely to a sensitivity to wheat. In other words, a sensitivity to the same food may manifest itself in producing edema of the mucous membrane of the bronchial tree in one individual, giant urticaria in another, a congestion of the nose in the third, and in the fourth, a local edema in some part of the brain. From a study of experimental anaphylaxis in the animal and clinical manifestations of allergy in the human, it seems logical to believe that the migraine patient has a localized edema of the brain due to a specific sensitization

to food in a similar way to that in which urticaria cases have localized edema of the skin, or asthmatics have localized edema of the bronchial *cul de sac*. After the local edema of the bronchial tubes, a hive on the skin, or a patch of eczema disappears, the area involved will show no structural changes. Likewise in an autopsy on a patient who has suffered from severe migraine for a number of years, no pathological changes can be detected.

DIAGNOSIS OF MIGRAINE

The direct diagnosis of migraine is based upon a history of familial headaches and in the majority of the cases a history of other allergic manifestations either in the antecedent who has the sick headaches or his blood relatives. It is aided by the history of other allergic manifestations in the individual and the direct history of paroxysmal recurrent sick headaches that started early in life, and manifested by a chain of symptoms which in the typical case is characterized by four stages—the prodromal, the aura, the attack, and the post-migrainous phase. During the prodromal stage the patient is either depressed or hyperactive and many note bulimia or a druggy sleep. Following the prodromal state the patient may develop the typical headache without preceding aura. Sensory symptoms are the rule. The most common sensory symptoms are scintillating scotomata, photophobia, hemianopsia (usually homologous), and paresthesia of the hands, feet or face. The majority of these sensory symptoms are contralateral to the hemicrania. Motor symptoms occur in approximately 50 per cent of

the patients, motor aphasia being the most common.

In a small percentage of the patients there may be mental confusion. Vasomotor symptoms are fairly common and may occur before the headache appears or during its course. In some cases there is flushing, in others pallor, or there may be general profuse perspiration. Occasionally we note inequality of pupils.

The headache, or third stage, develops as a rule along with some of the sensory or motor aura, but as stated above may develop without any preceding sensory or motor symptoms. It varies in degree and location but in the great majority of the patients it is a hemicrania, and in approximately 50 per cent of the patients it starts as a hemicrania and becomes generalized. At one attack the headache may be a pure hemicrania and in a subsequent attack start as a unilateral headache and become generalized. Along with the headache the patient usually develops nausea, which may or may not be followed by emesis. As a rule emesis is more common in the early years of the headache.

The duration of the attack may extend from a few hours to several days, may alternate from side to side, and as the headache wears off the patient passes into the post-migrainous stage characterized by exhaustion, sleepiness, polyuria, or nasal irritation.

The direct diagnosis of migraine is established when relief is obtained by removing specific foods from the diet and symptoms recur on deliberate partaking of these foods. It is preferable that these foods be removed and added without the patient's knowledge.

Physical findings are more valuable to rule out the presence of other conditions than to establish the direct diagnosis. The laboratory findings in the typical case will be of little value in confirming the diagnosis of migraine. Testing by the scratch and intradermal methods will reveal positive reactions to various foods or other foreign proteins in practically 100 per cent of the cases.

DIFFERENTIAL DIAGNOSIS

All cases of migraine are cases of headache, but not all cases of headache are migraine. The syndrome must be differentiated from functional headache, trifacial neuralgia, myalgia, intoxications, such as those of alcohol, tobacco and uremia, and from headache due to a brain tumor or pituitary dysfunction. As a means of differentiating migraine from pituitary headache Engelbach²⁸ states:

"The diagnosis of pituitary headache, however, cannot be made upon the characteristic location, severity of pain and associated ocular or gastric symptoms. There must be sufficient other evidence of pituitary disorder, such as osseous, genital, dermal or pigmentary changes, accompanying these headaches to warrant such a diagnosis."

Tierney²⁹ states:

"... our cases of pituitary headache have been more often found in individuals with other signs of pituitary disturbance; have been bilateral, nonparoxysmal, associated with different ocular manifestations, if any, and not usually accompanied by nausea and vomiting."

Migraine associated with vomiting is not uncommon. More than one patient with migraine has lost his normal appendix due to a mistaken diagnosis. A clear cut history of periodic headache occurring since childhood or young

adult life, with perfect freedom between attacks, especially if there is an ancestral history of allergy, spells migraine. A differential diagnosis of cases in which the headache is of recent origin is more difficult. The average physician probably would not think of migraine as a diagnosis in a child coming with a complaint of periodic headache. In all probability the child would be sent to the oculist or rhinologist for investigation. Even the pediatrician frequently forgets that migraine is common in childhood.

About 50 per cent of our cases developed migraine before 15 years of age. About 7 per cent of all people have migraine sometime in life. In other words, at least 2 per cent of all children during the first decade suffer from migraine. In making a differential diagnosis a family history of allergic conditions should be given much weight. One should be careful of making a diagnosis of migraine, however, in one whose symptoms appear after 40 years of age unless the family tree is filled with allergy. Migraine, like other allergic diseases, is not always typical. In an atypical case with a family history filled with allergy one would probably not err in making a diagnosis of migraine. On the other hand, if the symptoms are not clear cut and there is no definite family history of allergy, one is not justified in making such a diagnosis.

PROGNOSIS

Timme⁶ states that with few exceptions migraine disappears in the fourth or fifth decade. From our study this appears not to be exactly true, since, of the 202 cases, 22 came

seeking relief during the sixth decade. From the standpoint of life and death prognosis is good. Many patients also have other allergic diseases. It is not uncommon for a patient to have his life seriously interfered with due either to the frequency, or to the severity, of migrainous attacks. Of our cases, 4, or 1.9 per cent, were not able to carry on a gainful occupation on account of the severity of the attacks, and in 10, or 4.9 per cent of our patients, their symptoms seriously interfered with their work.

TREATMENT

Treatment should consist of *first*, pre-marital advice; *second*, thorough elimination of predisposing factors; *third*, careful investigation and elimination of the exciting factors; and *fourth*, treatment of the attacks.

Pre-marital Advice. It is certainly the duty of a family physician or specialist dealing with migraine to instruct the parents of allergic children concerning the possibility of the transmission of the disease. A young man with migraine who marries a girl with migraine or some other allergic syndrome, or one whose family tree is saturated with allergy, may expect some form of allergy to appear in about three-fourths of his children.

Predisposing Factors. Until the last decade much attention was given to the predisposing factors, as little was known about the exciting ones. Predisposing factors should be determined and eliminated. For example, plenty of rest and sleep should be taken by the sufferer; avoidance of physical exhaustion and mental fatigue and worry is always in order. Toxic states should be investigated and eliminated if

found. Correction of refractive errors and any error of the special senses should be done.

When all the foregoing measures have been taken many patients will be some better but not until the exciting factors, namely, the foods to which they are sensitive, are found and removed, can one hope for good results.

Elimination of Exciting Factors. In our present series of 202 cases, who have been treated by specific food eliminative measures, 44, or 21.7 per cent, received either total, or more than 80 per cent, relief, which we consider excellent results. Another 76, or 37.6 per cent, received between 60 and 80 per cent relief, which we count good results, and another 58, or 28.7 per cent, received from 40 to 60 per cent relief, which we consider fair results. Twenty-four cases had but little or no relief.

From our findings it appears that the results in the treatment of migraine are as good or better than those obtained in nearly any other chronic disease. The average patient who receives more than 80 per cent relief, practically speaking, is well, as the symptoms interfere little with his comfort, the comfort of his family, or his ability to carry on a gainful occupation. Frequently those who receive more than 60 per cent relief are extremely grateful because they realize that their unhappy, uncomfortable, unpractical condition has been greatly changed. Diet manipulation based on specific sensitization to food findings seems logical, is practical, and there is no element of danger in it.

Treatment of the Attack. For those cases who have prodromal symptoms

appearing the day before the actual attack, manifesting themselves by irritability, nervousness, abnormal appetite, etc., carbohydrates and sugars should be restricted in the diet; a saline cathartic should be given; and but little or no evening meal should be taken. The following morning if the attack actually appears, no breakfast should be taken, and if the stomach will permit, a second mild saline cathartic should be given. The noon lunch should be a light one. Sugars and carbohydrates should be restricted. Some sufferers feel better lying down without too much light in the room.

As many remedies as there are drugs in the Pharmacopeia have been suggested for the relief of pain during the attack and in only an occasional attack do they really do much good. Morphine and codeine should be used as the last resort. Barborka³⁰ has suggested the use of the ketogenic diet. With such a method the patient is kept in a state of ketosis. From an allergic standpoint such a diet in some cases should relieve the patient from symptoms, or partially relieve him, as there would be removed either entirely or in part the foods to which he is specifically sensitive. To keep a patient in a state of ketosis for a chronic disease like migraine seems rather severe, as there is surely an element of danger. An eliminative diet based on a study of the foods to which the patient is specifically sensitive on the whole gives results equal to those of practically any other chronic disease.

CONCLUSIONS

1. Migraine appears to be common in childhood since nearly one-third of

all cases studied developed symptoms during the first decade.

2. The syndrome is more common in business men, professional men, and teachers, than in laborers.

3. About seven per cent of all people in the United States sometime in life suffer from the symptom complex.

4. Like asthma, symptoms of migraine in childhood may vary greatly from those of the adult. Gastric symptoms are usually marked.

5. Migraine is interchangeable in the linkage with other allergic syndromes.

6. A family history of allergic diseases was elicited in 167 out of 202 cases, or 82.1 per cent.

7. Of the 202 cases studied 81.1 per cent suffered from other allergic syndromes.

8. From our findings it was concluded that the exciting factor in all cases of migraine is a specific sensitization.

9. There are many predisposing factors which should be investigated and eliminated.

10. The pathology in migraine is probably a local vasomotor dilatation producing a local congestion of the brain corresponding to a hive on the skin.

11. A familial history of allergy or a history of allergic manifestations in one who suffers from headache aids but does not establish a diagnosis of migraine.

12. The treatment of migraine based on allergic findings gives results equal to the treatment of practically any other chronic disease.

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Diet As a Factor in the Etiology of Anemia*†

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JUST as the body strives to preserve a constant composition of other important factors in the internal environment so, too, the red cell and hemoglobin content of the blood is maintained at a normal level even under very adverse circumstances. When human beings^{1,2,3} or animals⁴ are subjected to prolonged and complete fasting, red cell and hemoglobin figures per unit volume remain at or near normal until long after marked general body wasting has taken place. In partial starvation, when food intake is below body needs, anemia does not occur until very late, provided the diet is reasonably diverse. For example, a hysterical woman, observed in the University Hospital, had in the course of 14 months starved herself to an extreme degree of emaciation: yet her blood showed 4,760,000 red cells and 78 per cent of hemoglobin. This is due in part to the careful hoarding and re-utilization of available material (as we know to be the case with blood pigment, and as is perhaps the case with cell stroma), and in part to the fact that the materials necessary for red cell and hemoglobin formation are abundantly present in a great variety

and number of foods. So anemia is uncommon in the rapid wasting of Grave's disease or severe diabetes. (The average red cell count in 100 cases of Grave's disease was 4,610,000; and the hemoglobin, 80 per cent. One patient lost 105 pounds in 12 weeks, yet his blood showed 4,600,000 red cells and hemoglobin 90 per cent.) It is safe to say that anemia results from dietary causes only when the diet is greatly restricted as to certain foods and then only when such a diet has been persisted in for a long time.

Much has been learned in recent years of the rôle of diet in blood formation. Especially the studies of Whipple, of Minot, and of their collaborators have demonstrated the quantitative effects of individual foods on red cell and hemoglobin production in various pathologic states. In the light of their findings we are better enabled not only to treat anemic conditions but also to evaluate diet as a factor in their production.

DIET AND SECONDARY ANEMIA

Diet plays its most conspicuous part in the production of secondary anemia. The essential feature is usually a diet poor in iron and other hemoglobin building foods. While anemia from this cause may occur at any age, there are certain times of life when it is more common. The condition first pre-

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sents itself, and with great frequency, in infancy. The normal infant born at term possesses a sufficient store of hemoglobin and iron to tide it over the lactation period until a more varied diet meets current blood-building needs. Should the infant have a deficient supply to begin with, or should the inception of mixed feeding be too long deferred, a hypochromic or secondary anemia will result. Pediatricians have, therefore, long recognized that nutritional anemia is most likely to develop in premature infants, in those underweight at birth, in twins, in those whose lactation period is too prolonged or who early develop abnormal eating habits. Abnormalities of gastrointestinal function can further add to the infant's troubles by interfering with absorption. Mackay⁵, on the basis of observations in 770 infants, concludes that the condition is essentially an iron deficiency which is curable by iron medication (iron and ammonium citrate) and preventable by the same means if treatment is started at the age of two months. She finds no evidence of a vitamin deficiency. Hill⁶ reaches similar conclusions but obtained quicker results by combining liver with iron therapy.

Adolescence is the next period in which we often see anemias due to a diet low in iron and in other hemoglobin building foods. Chlorosis is the most marked example of this group, and while other factors are possibly concerned in its etiology, one cannot help but feel that the virtual disappearance of this condition in the last few decades is largely due to the better hygiene of diet and exercise in modern youth. In its place, however,

there are seen an increasing number of chloro-anemias in middle age, chiefly in women, due to a diet low in iron, in meats and vegetables, high in carbohydrates, and aptly called by Minot the "Soda Lunch Diet". To recognize the true nature of these cases clinicians should investigate with greater care than heretofore the diet habits of their patients and, in order to advise them intelligently, should familiarize themselves with the rôle of diet factors in hemoglobin construction as so thoroughly worked out by Whipple and his collaborators^{7,8}.

Lack of vitamins has been suggested as a possible cause of anemia. Here the evidence is as yet meager and contradictory. Experimentally, Happ⁹ found that rats kept for a long period on a diet low in anti-rachitic substance became anemic. Secondary anemia was observed by Sartori¹⁰ in pigeons deprived of vitamin B and in guinea pigs on a diet low in vitamin C; and a pernicious type of anemia by Wills and Mehta¹¹ in rats on diets with no vitamin C and almost no vitamin A. On the other hand, no effects on red cells or hemoglobin were noted by Sherif and Baum¹² in rats deprived of vitamins A, B, C and D; or by Cartland and Koch¹³ in rats deprived of vitamins A, B, and E; or by Sure, Kik and Walker¹⁴ in vitamin B or E deficiency in rats. Clinically, Koessler and Maurer¹⁵ have claimed that 75 per cent of patients with severe anemia give a dietary history of vitamin deficiency, and Aron¹⁶ calls attention to the fact that anemia in children is often associated with scurvy. However, Keefer and Yang¹⁷ and Pillat and Yang¹⁸ in observations on anemia asso-

ciated with various clinical avitaminoses point out that in the majority of instances the diets of these individuals have been deficient in hemoglobin-building substances as well. It is conceivable, however, that an associated avitaminosis could aggravate the anemia-producing effect of a diet also deficient in red cell and hemoglobin-building materials.

The claim that a copper deficiency may play a part in causing secondary anemia has not been substantiated. Whereas Waddell, Steenbock and Hart¹⁹ found that of 13 metals copper alone, when added to iron, cured anemia in young rats caused by a whole milk diet, Drabkin and Waggoner²⁰ cured such animals by a synthetic diet containing less copper than the original milk diet.

Brief mention is made of a form of nutritional anemia that has attracted considerable attention especially in Germany in recent years. In 1916, Schelltema^{20a}, and in 1918, Schwenke²¹ independently reported cases of anemia in infants fed on goat's milk and since then numerous similar observations have been recorded. The blood picture is usually that of secondary anemia, but in a considerable minority of cases there is present an anemia pseudo-leukemica^{22,23} with severe anemia, high color index, macrocytosis, nucleated red cells, leukocytosis, pallor and an enlarged spleen, and which Stoeltzner²² refers to as possibly an infantile form of pernicious anemia. The cause of the anemia is not certain. Brouwer²⁴ points out that it is probably not an iron deficiency, for the anemia develops at an age before the infant normally exhausts its iron store. While goat's

milk has been found quite low in vitamin C^{25,26}, the addition of vitamins to the diet is not effective²⁷, and puppies fed on goat's cream and cow's skimmed milk become anemic²⁸. It is, therefore, probably not an avitaminosis. The myelotoxic action of certain fatty acids abundantly present²² offers perhaps the best explanation. An unknown constitutional factor has also been invoked²⁹. A change to cow's milk diet is curative.

DIET AND PERNICIOUS ANEMIA

Since Biermer³⁰ in 1872 in his original communication on progressive pernicious anemia expressed the opinion that insufficient and unsuitable food was a factor in its etiology, much has been written of the possible relation of diet to this disease. However, not until the announcement by Minot and Murphy³¹ of the treatment by liver feeding was any real progress made in this direction.

As a basis for the discussion of the relation of diet to pernicious anemia attention is called to the hypothesis of etiology which has been proposed by Castle, Townsend and Heath³² as a result of their excellent studies on the nature of the reaction between normal human gastric juice and beef muscle in producing a substance that leads to clinical improvement in pernicious anemia, similar to the effect of liver feeding. Briefly stated, the interaction of an *intrinsic factor* (an as yet unidentified substance, secreted by the normal gastric mucosa, and not present in patients with pernicious anemia) and an *extrinsic factor* (in the diet, probably protein in nature—e.g., beef muscle—or closely related) results in a

substance (or substances) which after absorption produces a marked hematopoietic effect in pernicious anemia. *Pernicious anemia is essentially due to the lack of the intrinsic factor.* The substance resulting from the interaction of the intrinsic and extrinsic factors exists preformed in liver and certain other foods, by the feeding of which, pernicious anemia may be successfully treated.

How may diet be related to this hypothesis?

1. In the first place, Castle, Townsend and Heath³² suggest that abnormal diets may possibly have a relationship to the original gastric dysfunction in pernicious anemics. This is as yet hypothetical.

2. In the second place, there are probably a great many more *potential* pernicious anemics than those who have actually developed the disease: individuals with probably a partial or possibly even complete loss of the intrinsic gastric factor; individuals who nevertheless have not become anemic because in their diets they manage to obtain enough of the *preformed* hematopoietic substance (liver, kidney, others?) to meet their needs. The well-known familial occurrence of achylia gastrica and pernicious anemia lends support to this view. In such individuals the deprivation of certain foods might be the means of precipitating or hastening the anemia. In Germany the period of greatest food lack as a result of the war and the financial crash was the year 1923. Protein food was particularly scarce. In that year Germany recorded its highest incidence of pernicious anemia. In the Clinic at Göttingen the number of

pernicious anemia patients in 1923 was seven times as great as in 1908, and three times the number in 1926^{16,33,34}, when the stringency had been largely relieved. Then again, in such potential anemics a diet which has just sufficed at a given age may become inadequate in later years, for Minot³⁵ has observed that, while an average of 300 grams of liver was an adequate daily maintenance dose for pernicious anemia patients at the age of 45, those at 60 required 600 grams and at 69 well over 600 grams, probably because of diminished absorption or utilization, incident to arteriosclerosis.

3. To the above I wish to add another possibility: namely, that in rare instances an Addisonian type of blood picture may result in a patient whose diet is deficient in the *extrinsic factor*. I wish to report a patient who in the presence of free hydrochloric acid in the gastric juice, developed an Addisonian blood picture; an anemia apparently brought on by an unusual type and degree of prolonged voluntary diet restriction and in which a more liberal diet produced a typical remission. The data available are unfortunately rather scant but perhaps not wholly inadequate.

CASE REPORT

Case I. T. O., an Irishman of 50 years, was admitted to the University Hospital on Sept. 20, 1921, with chief complaints of weakness, swelling of the legs and dimness of vision. At the age of 34 he had become a vegetarian in the ordinary sense of that word, using milk and eggs freely in the diet. After some years, however, he became convinced that this was inconsistent, so he avoided milk and eggs. He then proceeded to distinguish between fine and gross vegetables, the latter being those for which animal excreta were used as fertilizer, (he

specified, among others, peas and beans) and these in turn he decided to use very sparingly. For these and other reasons he became estranged from his wife and thereafter lived alone in an apartment where he prepared his own food. He worked long hours as a teacher and magazine writer, and eating was only of minor significance in his scheme of things. For example, he would boil a huge pot full of potatoes and spinach on Sunday and would eat these cold the rest of the week, together with plenty of fruits, raw vegetables, bread and nuts. In the past six years there had been gradually increasing distress after meals, failing vision, diminishing appetite and an increasing constipation. In the past year these symptoms had become aggravated and in addition there had developed weakness, swelling of the feet and ankles, dyspnea on exertion, and, more recently, numbness and tingling in the feet. His weight had fallen from a maximum of 125 pounds to 115. He did not complain of a sore tongue.

Physical examination showed a pale pasty-looking individual with markedly swollen legs. There was no jaundice of skin or sclerae. The tongue was smooth and pale. The spleen was not palpable. Knee jerks and Achilles jerks were preserved but diminished. Vibratory sense was unfortunately not tested. An eye examination showed optic atrophy, a central color scotoma, marked contraction of the retinal arteries, vision 3/60—(in 1916 it had been 6/6 according to the ophthalmologist's record). During the first two weeks in the hospital the temperature rose as high as 100.4° F.; thereafter it remained normal. The urine had a specific gravity of 1010, contained no sugar and no albumin; the urinary sediment showed occasional hyaline casts, no blood or pus. The feces contained no occult blood.

The blood figures are shown in table I and chart 1.

The blood picture with its high color index, red cell changes and leukopenia suggested a pernicious anemia. In view of his serious condition a transfusion was decided upon. The patient, however, refused to accept blood unless it were from another vegetarian and one who did not use to-

bacco! Iron was ordered, but unfortunately in the form of "ovoferrin", which the patient refused because of the "ovo". He did receive several hypodermics of iron and arsenic but finally refused them because of discomfort at the site of injection. He thereafter received no medication. Because it was felt that his anemia had been caused by his bad diet habits, it was decided to feed him white meat of chicken, milk, and eggs. This had to be done surreptitiously by disguising these foods in various combinations with vegetables. There resulted a marked and rapid improvement in the patient's general condition as well as in the blood picture. His vision improved to the extent that he could again read with the aid of a hand lens. The edema, obviously due to protein starvation, promptly disappeared, while his weight increased to 120 pounds. On Jan. 7, 1922, the patient left the hospital and returned to his work.

For several months he continued in fair health. But he returned to his original diet habits and eventually began to fail again. A gastric analysis made in March, 1922, showed a total acidity of 30 and a free hydrochloric acid of 18. In April, 1922, the blood count had again fallen to 1,400,000 and the hemoglobin to 35 per cent. He was urged to return to the hospital, but he refused, going instead to a vegetarian sanitarium in another city where he died a few weeks later.

In the light of present knowledge, it seemed to me that this was a case in which an addisonian type of blood picture had resulted from a diet so restricted as to be insufficient in the *extrinsic factor* necessary for interaction with normal gastric juice to produce the substance which stimulates hemopoiesis in pernicious anemia; a case in which the feeding of a diet adequate in animal protein produced a characteristic remission.

I therefore reviewed the case histories of all anemic patients that had been in the University Hospital with particular reference to their dietary

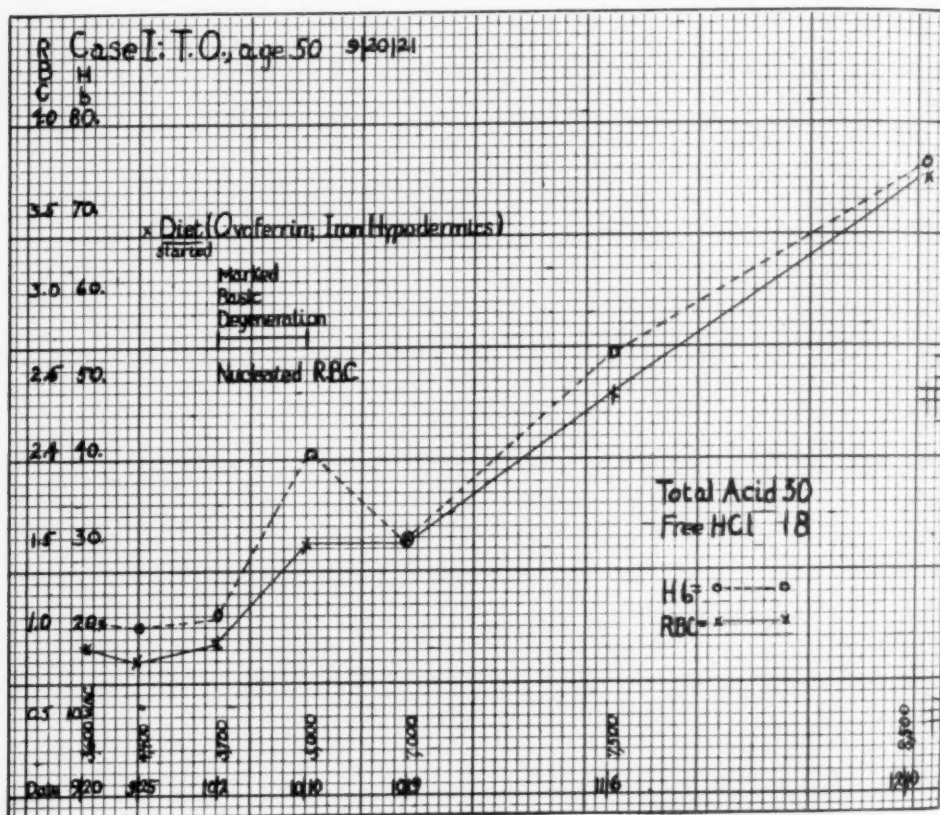


CHART I

TABLE I
Blood Findings in Case I.

Date	R.B.C.	Hb. %	Color Index	W.B.C.	Neut.	Lymph.	Mono.	Eosin.	Remarks
9/20/21	910,000	21	1.16	3,600	45	55	1	1	Slight polychromatophilia, marked anisocytosis, marked poikilocytosis, no nucleated r.b.c., no basic degeneration.
9/25	810,000	20	1.23	4,900					No basic degeneration; no nucleated r.b.c.
Surreptitious feeding of chicken muscle, eggs, and milk begun									
10/2	920,000	21	1.15	3,700					Marked basic degeneration; nucleated r.b.c. present.
10/10	1,500,000	41	1.37	5,000					Some basic degeneration.
10/19	1,500,000	30	1.0	7,000					
11/6	2,400,000	52	1.08	7,500					
12/10	3,700,000	75	1.01	8,500					"Cells look normal."

habits. These included 183 cases of pernicious anemia, 164 cases of secondary anemia and 25 cases of chlorosis. Of the chlorotics, 6 gave a history of poor dietary habits preceding the onset of anemia, but none of a degree that could be interpreted as possibly deficient in the sense of case I. In none of the secondary anemia cases was a marked diet deficiency noted. In two cases diagnosed as pernicious anemia the evidence was suggestive.

CASE REPORT

Case II. R. G., a Porto Rican woman of 55, was admitted to the University Hospital on Oct. 15, 1929, with a chief complaint of weakness. After the death of her husband 4 years before, she had become worried and depressed. For the past 3 years she had eaten no meat, practically no vegetables, and had limited her food largely to white bread, milk and coffee. She gradually became weaker and her weight fell from 165 to 136 pounds. She did not have any paresthesias. There were periods of looseness of the bowels. The past history included an attack of filariasis ten years before.

Physical examination showed some pigmentation of the skin. The tongue was smooth and atrophic. Vibratory sense was not tested "because of linguistic difficulties." Reflexes were not mentioned. The spleen was not enlarged. There was some edema of the legs. The urine was not abnormal. The

van den Bergh test gave a negative direct reaction and an indirect reading of 0.65 unit. Fragility of the red cells was within normal limits. A fractional gastric analysis showed a maximum figure of 68 for total acidity and of 34 for free hydrochloric acid.

The blood findings are given in table II.

The blood picture was that of addisonian anemia, and the feeding of liver extract produced a typical remission. The patient left the hospital on Oct. 31, 1929, and has not been heard from since then. During her stay in the hospital she had no diarrhea, but rather a moderate constipation.

Case III. T. B., a white man, aged 75, was admitted to the University Hospital on April 30, 1925, with a chief complaint of weakness and swelling of the legs. Ten years before he had been sent to the penitentiary where he had been until the day of admission. Nine years ago he had begun to have attacks of indigestion with epigastric distress and belching of gas and sour material. He then restricted his diet, avoiding all meat, beans and potatoes. The indigestion attacks became less frequent but did not cease, so he further restricted his food in quantity and quality. In the past year he had become weaker, emaciated and obviously anemic, with more recently edema of the legs and increasing constipation. He was finally sent to the hospital because of suspected gastric cancer.

Physical examination showed an emaciated old man weighing 98 pounds. There was a slight yellow tinge of the skin. The superficial arteries were sclerotic. The tongue was not described. The heart was negative

TABLE II
Blood Findings in Case II

Date	R.B.C.	Hb. %	Color Index	W.B.C.	Neut.	Lymph.	Mono.	Eosin.	Remarks
10/14/29	2,900,000	65	1.12	3,600	31	65	2	2	Some poikilocytosis and polychromatophilia. Slight anisocytosis. No nucleated r.b.c.
10/19	Liver extract, one vial t. i. d.								
10/22	4,000,000	84	1.05	3,200					
10/23	3,600,000	91	1.26	4,000					
10/25	3,800,000	95	1.25	5,100	53	41	4	2	Macrocytosis; slight aniso- and poikilocytosis. Reticulocytes, 4.2 per cent.

and the pulse rate normal. The spleen was not palpable and the peripheral reflexes were normal. The blood pressure was normal. There was moderate edema of feet and legs. The urine contained no sugar and no albumin, and the urinary sediment was negative save for occasional hyaline casts. A complete gastrointestinal x-ray study was negative. Fractional gastric analysis showed a maximum of 98 total acidity and 53 free hydrochloric acid. The van den Bergh test gave a negative direct reaction and an indirect reading of "a trace". There was some increased fragility of the red cells, hemolysis beginning at 0.5 and being complete at 0.375. The blood counts are given in table III.

TABLE III.
Blood Findings in Case III

Date	R.B.C.	Hb. %	Color Index	W.B.C.	Neut.	Lymph.	Mono.	Eosin.	Remarks
5/1/25	2,880,000	65	1.14	8,250	53	40	6	1	"No reticulocytes."
5/17	2,750,000	50	0.91	4,800					
5/23	2,800,000	65	1.16	7,600	40	50	6	4	

The diagnosis, which the attending physician recorded as pernicious anemia, while made apparently by a process of exclusion, has little to support it in the data at hand. No description of the blood smears are found in the record. No treatment was given and his condition at the time of discharge was unimproved. His subsequent fate could not be learned.

The blood findings in cases II and III are graphically shown in chart 2.

In the light of case I, meager though the data are, it is suggested that in rare instances an addisonian blood picture may result from a diet so unusually restricted, especially in animal protein, as to be deficient in the *extrinsic factor* necessary for erythropoiesis.

Two objections must, however, be considered. In the first place, to what extent was the diet of these patients deficient in other respects? Certainly in case II, and probably in case III, the diet was deficient in iron, as well as

in vitamins, especially in vitamins B and C. In both of these patients, therefore, it must be admitted that the anemia was due, in part at least, to these factors. In case I, however, the diet covered a considerable range of vegetable foods, and many of these in the raw state, so that it seems unlikely that the diet was to any great degree deficient in any vitamins or in hemoglobin-building foods. An intelligent and educated person,—he was a Doctor of Philosophy—the patient

well knew the need of diversification in diet, and this he conscientiously sought to achieve within the limits of his convictions. Protein lack would appear to be the outstanding, and perhaps the only defect in this patient's diet.

Then there is lacking a further important proof: namely, that the gastric juice in these cases actually did contain the *intrinsic factor*. The presence in all three of these patients of free hydrochloric acid in the stomach contents may be suggestive but is of course no proof of the presence of the *intrinsic factor*. Castle, Townsend and Heath³² have observed two cases of pernicious anemia with free hydrochloric acid in the gastric juice, which juice was nevertheless ineffective on incubation with beef muscle. But the fact that in case I the feeding of chicken muscle, milk and egg (foods which do not contain the erythro-

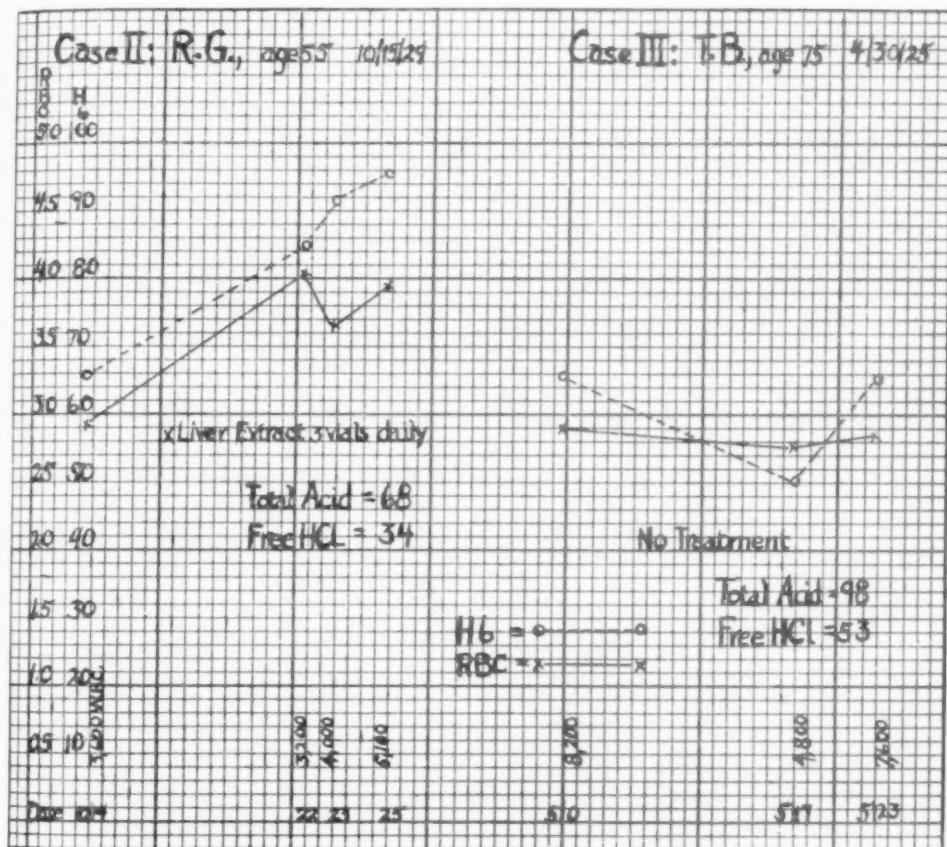


CHART 2

poietic stimulant in a preformed state) produced a typical remission, at least suggests the presence of the *intrinsic factor* in that patient's gastric juice.

The production of an addisonian blood picture in the manner suggested must be exceedingly rare. So Willson and Evans³⁶ in their series of 111 cases of pernicious anemia noted no significantly abnormal eating habits. A search of the literature has failed to reveal a case quite comparable with that of our first patient. O'Hara and Greval³⁷ reported typical pernicious anemia in a boy of 14, who had lived

largely on bread, milk, potatoes, and candy. Here there may well have been an avitaminosis, as well as iron deficiency. Furthermore, the patient had a true achylia. Avitaminosis undoubtedly also played a part in Aykroyd's³⁸ patient, a woman of 39, with edema and a suggestive blood picture following six months' subsistence on dry bread, molasses, tea and occasionally a little salted meat, and with a history of beriberi 15 years before. The diets of Hindu women with so-called pernicious anemia of pregnancy, reported by Wills and Talpade³⁹, while very low

in animal protein, were also low in vitamins A to C, to which deficiency the authors attribute the anemia. In short, it would seem to occur only in a "super-vegetarian", such as was our patient.

SUMMARY

1. Anemia from dietary causes results only when an unbalanced diet has been persisted in for a long time.

2. The usual result of such an unbalanced diet is a secondary type of anemia, a chloroanemia.

3. The diet fault in these cases is (a) most commonly a lack of iron and hemoglobin-building elements; (b) rarely perhaps a lack of one or more vitamins, or a combination of (a) and (b).

4. The development of pernicious anemia may perhaps be hastened by diet restrictions (probably of certain animal proteins) in those with achylia gastrica (partial or complete lack of intrinsic factor for stimulating erythropoiesis).

5. The combination of avitaminosis, low protein and iron intake may possibly at times produce an addisonian blood picture (case II, III?).

6. In rare instances an addisonian blood picture may result from a diet inadequate, through prolonged protein starvation, in the extrinsic factor, which is necessary for the formation of the substance for stimulating erythropoiesis (case I).

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Anemia Associated With Gastrointestinal Disorders: Clinical Considerations and the Value of Iron in Treatment*†

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THE relationship between disorders of the gastrointestinal tract and anemia is of considerable importance because it is common, and in some instances the anemia resembles that seen in pernicious anemia. The conditions attracting most attention have been achylia gastrica, sprue, *Dibothriocephalus latus* infestation, multiple intestinal strictures, gastrectomy, hookworm infestation, and the chronic diarrheas. In the past, it has been customary to attribute the anemia to "toxic factors" and most of the cases have been studied from that point of view. In recent years, with the discovery of liver as a potent factor in the treatment of pernicious anemia¹ many of these conditions have been reinvestigated in an attempt to gather more precise information regarding the various factors responsible for the anemia and to evaluate the various therapeutic agents which are most beneficial.

At this time, twenty patients with

anemia associated with chronic dysentery, seven patients with anemia associated with hookworm infestation, and four patients with anemia associated with tuberculosis of the intestine are discussed. No attempt will be made to deal with the question of the relationship between disturbances in gastric function and anemia except to point out that since the recent important work of Castle and his associates² in pernicious anemia, the relationship of faulty gastric function to other forms of anemia is becoming better appreciated. The observation of Strauss³ in the anemias of pregnancy and Mettier and Minot⁴ and Waugh⁵ in chlorotic types of anemia indicate that disorders of gastric function may be of importance in some anemias other than pernicious anemia. However, before final conclusions can be drawn regarding the precise relationship between achylia gastrica and anemias, further observations are necessary.

ANEMIAS ASSOCIATED WITH CHRONIC DYSENTERY

Twenty patients with chronic dysentery and anemia have been studied. The diagnosis of dysentery was made

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from the clinical picture, culturing the organisms from the stools and finding the characteristic ulcers in the sigmoid on direct examination. All were due to bacillary infection. In the group as a whole all of the features which are characteristic of pernicious anemia were observed. There was atrophy of the papillae of the tongue in nine, gastric anacidity in four, combined system disease in two, retinal hemorrhages in two, and the blood picture of pernicious anemia in five. Other interesting clinical features were the presence of conditions associated with food deficiency in the form of edema disease in six, peripheral neuritis in two, hyperkeratosis follicularis in two, keratomalacia in two, and pellagra in one.

Etiology of Anemia. In considering the various factors responsible for the anemia, the duration of the diarrhea, the character of the diet, the changes in gastric secretion, the presence or absence of intestinal hemorrhage, and infection were analyzed.

In all of the twenty cases, the diarrhea had been present for two months or longer. It was evident, however, from the study of a number of other patients with chronic dysentery that factors besides the duration of the diarrhea were of importance in producing an anemia because only about twenty per cent of all patients with chronic dysentery develop an anemia. As a result of this observation it was necessary to study the question further in order to determine why anemia was present in some and not in others. As many patients with diarrhea had restricted their food intake and since this increased the nutritional disturbance,

the diets of the patients with anemia were investigated with care. It was evident that eighteen of the twenty patients had been on diets which were inadequate both in quantity and quality and it was noteworthy that the two patients who had not definitely restricted their diets had a gastric anacidity. From these observations it was concluded that anemia was more common in the patients with a chronic diarrhea and a restricted diet than in those who had a chronic diarrhea and a normal diet. On the other hand, if in the presence of a continuous diarrhea, the diet were not restricted, this did not necessarily protect the patient from anemia if gastric anacidity were present. But since gastric anacidity was present in only three of the patients with anemia, it was clear that it was not responsible for the anemia in the group as a whole. In one patient the secretion of acid was only temporarily disturbed; in the other two the anacidity was permanent.

A factor of importance in enhancing the anemia was blood loss. In all of the patients, a few red blood cells were present in the stools. In none of the patients, however, was there a history of a large hemorrhage and none was observed. Furthermore, the anemia improved in spite of continued slight loss of blood when the proper therapy was employed. It appeared, therefore, that blood loss was only a contributory and not the essential factor in producing the anemia.

The relative importance of the dysenteric infection in the sense of a bacterial intoxication was difficult to evaluate. As the anemia did not develop in all patients with chronic dys-

entery, and since the anemia improved following various forms of treatment in spite of the persisting dysentery, it is unlikely that infection was of importance as a direct cause but operated indirectly because it caused an ulcerative colitis and diarrhea which interfered with nutrition.

From these observations it is concluded that the anemia associated with

stances secreted by the worms, or to infection following the intestinal lesions produced by the worms. There is another factor of importance in any consideration of the etiology of the anemia, namely, malnutrition. In this study, seven patients with hookworm infestation and anemia were observed who recovered from their anemia without the removal of the worms. This

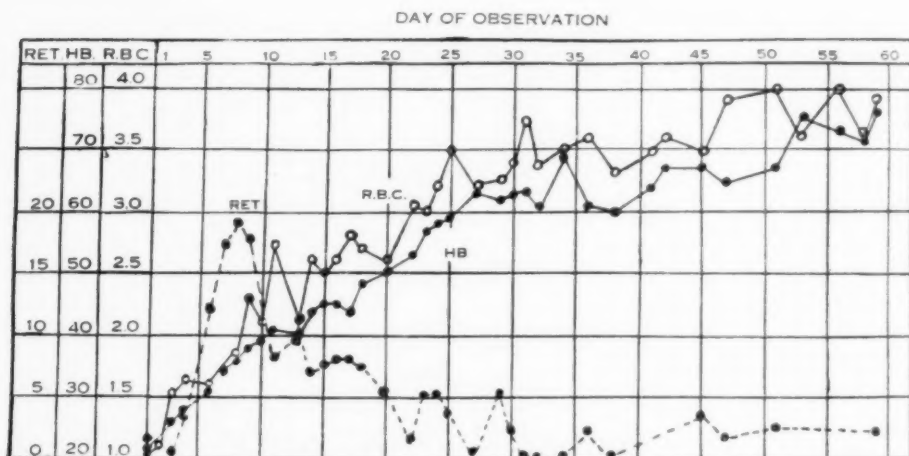


CHART 1. Patient with anemia associated with chronic dysentery recovering following an adequate amount of food.

chronic dysentery results from nutritional disturbances which are due to chronic diarrhea and inadequate diets. The part contributed by blood loss, disturbances in gastric function, and infection are not essential. Chart 1 illustrates the response of the blood in a patient following an adequate diet.

ANEMIA ASSOCIATED WITH HOOKWORM INFESTATION

The cause of the anemia associated with hookworm infestation remains obscure. In the past, it has been customary to attribute the anemia to chronic blood loss, hemolytic sub-

was accomplished by giving an adequate diet and iron. Liver also was found to be effective in accelerating blood regeneration, but its effect was less conspicuous than iron. All of the seven patients had a light worm burden, although the anemia was marked. This might lead one to believe that in these particular cases, the anemia had a different origin than usually occurs in hookworm infestation. Such an explanation is extremely unlikely and it is well known that although the majority of patients with hookworm infestation and anemia have heavy infestations, there are striking exceptions in which

anemia is present with a few worms, and conversely no anemia may be present with many worms. In view of these observations, factors other than the worm burden must be considered in explaining the anemia that is associated with hookworm infestation. Darling, Barker, and Hacker⁶ called attention to malaria and malnutrition as factors in explaining the severity of some cases and, more recently, Shapiro⁷ has discussed the discrepancy between the degree of anemia and the worm burden in two groups of patients with hookworm infestation, and emphasized the importance of nutritional factors in influencing the development of anemia. From a study of the literature and these seven cases, there appears to be no question but that Shapiro's observations are correct. It is necessary, therefore, to study factors other than the worm burden in any investigation of the anemia of hookworm disease.

The recent observations of Wells⁸ require comment. By direct observation, he has shown that the hookworms attached to the intestine of dogs withdraw blood from the intestine and eject it into the lumen in such a way that it is lost. He suggests that this blood loss is responsible in part at least for the anemia observed in hookworm infestation.

It has been generally recognized that blood loss is of importance in contributing to the anemia in many of these patients and it probably plays a part in many. In the patients whose blood returns to normal following adequate therapy for anemia, in spite of the fact that they continued to carry the worms, there must be other conditions respon-

sible for the anemia. It is likely, therefore, that while chronic blood loss is responsible for a part of the anemia in some of these patients such factors as malnutrition are of greater importance.

Chart 2 illustrates the response of a patient with anemia associated with hookworm infestation recovering following the feeding of liver and iron while he continued to carry the worms.

ANEMIA ASSOCIATED WITH TUBERCULOSIS OF THE INTESTINE

Tuberculosis of the intestine of the ulcerative type is frequently associated with anemia. Observations have been made on four patients with diarrhea resulting from tuberculous enteritis. In all there was an anemia and evidence of malnutrition and deficiency disease. In order to gather more information regarding the influence of nutritional disturbances in producing the anemia apart from the restrictions of the diet, the records of forty-two patients with tuberculosis of the intestines proven at necropsy were studied. The results of this study have been recorded in detail elsewhere⁹. It was found that the patients with ulceration of the intestines with diarrhea, or alternating constipation and diarrhea, were the ones who developed anemia most frequently, whereas if the intestinal function was not definitely disturbed throughout the course of the illness, anemia occurred no more often than in fatal cases of pulmonary tuberculosis without intestinal ulceration, or in cases of hyperplastic cecal tuberculosis. It appears, therefore, that the presence of diarrhea is an important factor that can lead to

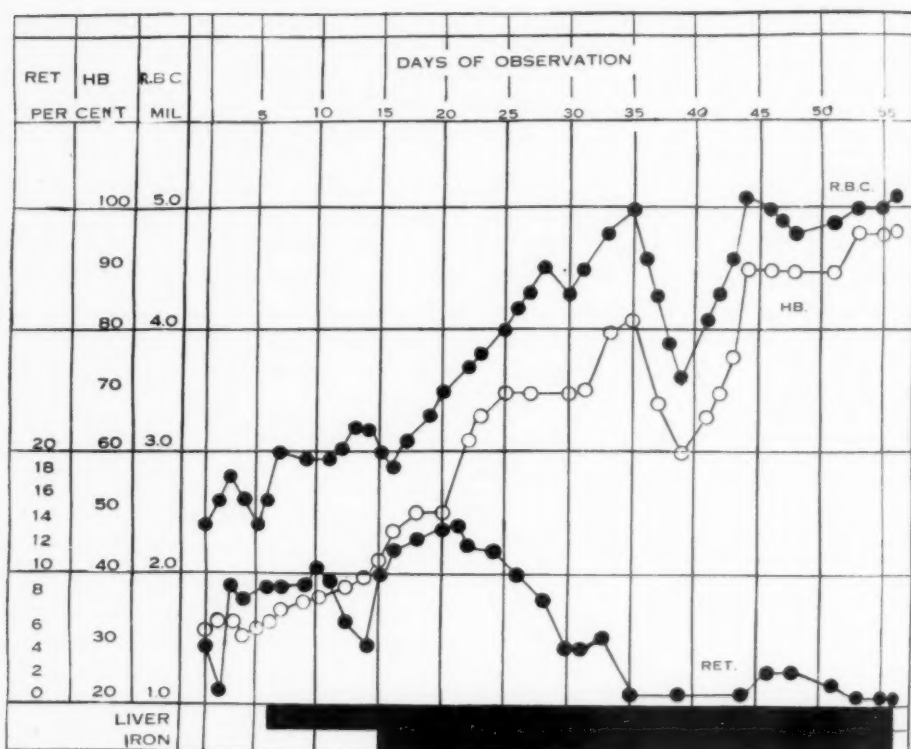


CHART 2. Patient with anemia associated with hookworm infestation recovering from the anemia following the feeding of liver and iron while he continued to carry the worms.

TABLE 1
Blood Findings in Patients With Tuberculosis of Intestines

Case Number	Red Blood Cells in Millions Per cu. mm.		Hemoglobin Per Cent		Reticulocytes Per Cent		Remarks
	Treatment		Treatment		Treatment		
	Before	After	Before	After	Before	After	
1	1.39	1.70	29	38	3.3	14.4	Keratomalacia Edema
2	3.08	4.22	58	81*	6.	2.2	
3	3.33	3.24	52	48	0	3.6	Edema disease
4	2.76	3.33	28	42	.6	4.	

*Improvement due to blood transfusion.

the development of anemia in these patients. Table 1 summarizes the blood findings of the four patients who were studied.

Chart 3 illustrates the course of the blood following treatment in a patient with chronic diarrhea due to tuberculosis of the intestines.

The occurrence of the various food deficiency disorders in the patients studied is of interest in supporting the thesis that the anemia was largely the result of nutritional disturbances. Keratomalacia, beriberi, edema disease, and hyperkeratosis follicularis were attributed to vitamin A deficiency, beriberi to a lack of vitamin B (G),

and edema disease to protein starvation.

In the interpretation of clinical features attributed to specific nutritional defects, it is essential to bear in mind that single food deficiencies seldom exist in man. In order that single food deficiencies may be studied in animals, the diets must be selected with meticulous care. When deficiency disorders exist in man, there is no such selection of food for the diet so that it is usually defective in a number of substances. This is apparent in any study of nutritional disturbances in man. It is not surprising, then, to find multiple nutritional defects in the same indi-

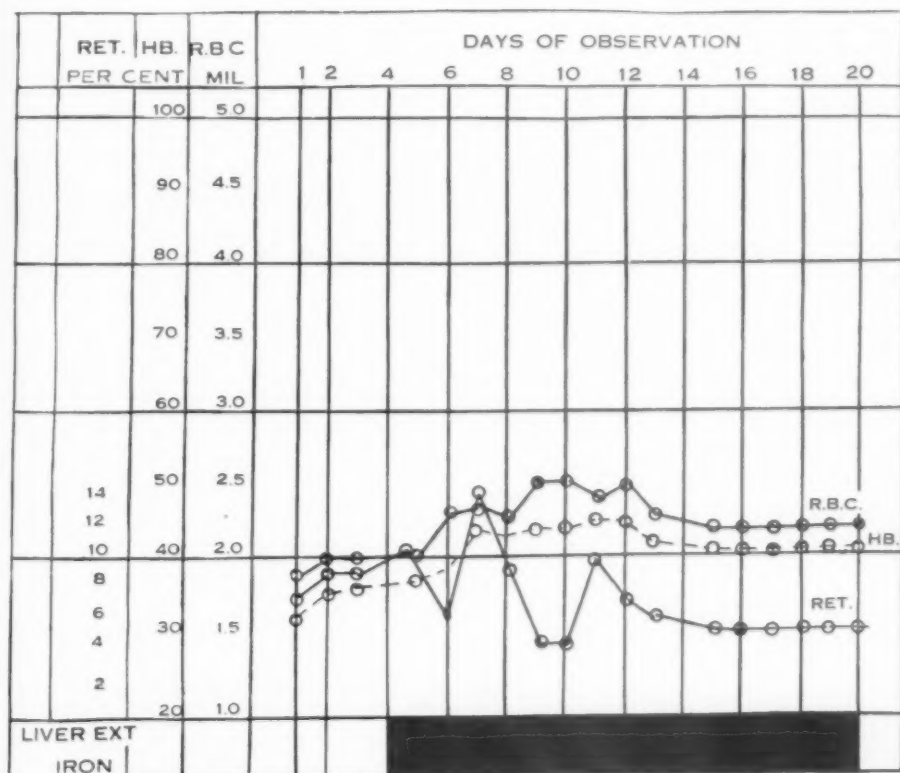


CHART 3. Patient with anemia associated with tuberculosis of the intestines showing no improvement following the feeding of liver extract and iron.

the red blood cell count, the higher the reticulocytes rose. There were exceptions among the patients with dysentery when the infection was so severe that death ensued, and when recovery followed blood transfusion. If any conclusions can be drawn from the data it would appear that the cases under discussion responded in the same way as those in which the anemia resulted from malnutrition. I feel, therefore that these observations lend support to the idea that the anemia in the patients with dysentery, hookworm infestation and tuberculous enteritis was of the same nature as that occurring in patients with malnutrition.

Observations of Mettier and Minot⁴ are of importance in emphasizing the value of optimum doses of iron in anemia resulting from chronic blood loss and restricted diets, and Strauss³ has described its effect in the chlorotic anemias of pregnancy with achylia gastrica, and Powers and Murphy¹¹ have reported positive effects in anemias due to chronic blood loss. My associates and I^{12,13,14} have found that iron was of value in the treatment of anemia due to chronic blood loss, restricted diets, anemia of pregnancy, chronic dysentery, hookworm infestation, chronic chlorosis, and some of the anemias of childhood. Furthermore, in some

TABLE 2
Cases of Anemia Treated With Iron

Diagnosis	Number Treated with Iron	No. Showing Improvement	No. Showing No Improvement
Dysentery	7	6	1
Hookworm	7	7	0
Tuberculosis of Intestines	4	0	4

In studying the response of the anemia to treatment it was plain that no single form of treatment produced a positive effect in all cases. For example, in the anemias associated with dysentery, positive responses were observed following liver extract potent for pernicious anemia, or iron, or various combinations of whole liver and iron.

The effects of iron therapy in some of the cases are instructive. It has been recognized for many years that iron is of value in the treatment of many forms of anemia, but recently an attempt has been made by various observers to define its usefulness with greater precision. The recent ob-

servations of Mettier and Minot⁴ are of importance in emphasizing the value of iron may be enhanced by the addition of whole liver.

The results of iron therapy are recorded in table 2. It was given in the form of ferrous carbonate pills ranging between two and five grams a day. The data clearly show that it was effective in the treatment of anemia associated with hookworm infestation, and in some of the anemias due to chronic dysentery. It was ineffective in the patients with tuberculosis of the intestine but in these patients no form of treatment was beneficial due to the severity of the infection.

The results of iron therapy upon the anemia associated with hookworm in-

festation were uniform and in some patients the effect was enhanced by liver. It is noteworthy that this could be accomplished while the patients continued to carry the worms. That iron is a valuable therapeutic agent in the treatment of anemia due to hookworm infestation is common knowledge and the papers of Day and Ferguson¹⁵, Dock and Bass¹⁶, Kobayashi¹⁷, Keefer and Yang¹², Keefer, Huang, and Yang⁹ furnish ample evidence to confirm this statement.

It is clear, then, that iron is a valuable therapeutic agent in the treat-

ment of some of the anemias associated with gastrointestinal disorders, but if it fails, other substances such as liver or liver extract should be administered.

SUMMARY AND CONCLUSIONS

Malnutrition is often an important factor in the production of anemia associated with disorders of the gastrointestinal tract such as chronic dysentery, hookworm infestation, and tuberculosis of the intestine.

Iron and liver therapy can accelerate hemoglobin regeneration in some of the cases.

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On the Morbid Anatomy of the Diaphragm*†

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THE diaphragm is probably the most interesting and important of all skeletal muscles. Its general physiological properties are unique¹; it plays a prominent part in a variety of functions of the body. Thus, it is the chief muscle of respiration, and it acts as an important circulatory muscle by propelling venous blood and lymph into the chest cavity. While the physiology of the diaphragm has received much attention, the pathology of this organ has been greatly neglected; with the exception of reports on diaphragmatic hernia and subphrenic abscess, there are but few studies concerning its morbid anatomy. Yet here, as in other organs, a thorough knowledge of morbid structure is a necessary pre-requisite to an understanding of the functional disorders attendant on disease.

It is true that there are relatively few disease processes which affect the diaphragm as primary lesions, but secondary lesions are extraordinarily common. The majority, though not all, of the diseases of the diaphragm are spread from adjacent tissues and

organs in intimate contact with it: the pleurae, the pericardium, the peritoneum, the liver, gall-bladder, stomach, spleen, adrenals, kidneys, pancreas and duodenum.

In the present communication are discussed some of the more common lesions occurring in the diaphragm, namely secondary neoplasm, tuberculous and acute inflammatory reactions, and certain degenerations. In all of these conditions the diaphragmatic muscle suffers impairment or destruction, and hence its function is interfered with to a greater or lesser degree.

NEOPLASMS

Primary tumors of the diaphragm are very rare. There have been reported less than a score of them, all of the connective tissue series: fibromas, chondromas, lipomas and sarcomas. Secondary tumors, on the other hand, are of far more common occurrence than is generally thought. Thus in a series of 164 pathologic diaphragms, I found eighteen secondary tumors. The growths were carcinomas in fourteen and sarcomas in three instances; the remaining tumor was a renal hypernephroma. Of the fourteen carcinomas, five were primary in the stomach, two each in liver, gall-bladder and ovaries, and one each in the lung, esophagus and small intestines. The sarcomas

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were two primary lymphosarcomas of the mediastinum, and one a spindle cell sarcoma of the thigh. In a series of 12 metastatic cancers of the diaphragm reported by Kitain², five were primary in the stomach, three in the breast, and one each in the uterus, gall-bladder, bronchi and tongue. Thus in both Kitain's and the present group of tumors the primary tumor was conspicuously most often located in the stomach.

In some of the cancers arising from the stomach, liver and gall-bladder it was difficult to decide whether the tu-

mors had spread to the diaphragm by direct extension or by metastasis. In the other tumors metastatic distribution was certain.

The gross appearance of the diaphragm varied considerably. In the cancers there was generally a diffuse flat-nodular infiltration beneath one or both serous surfaces (figure 1). Since the majority of these tumors had their primary seat in abdominal organs abutting on the diaphragm the peritoneal surface was generally more heavily infiltrated than the pleural surface. Microscopic examination showed the

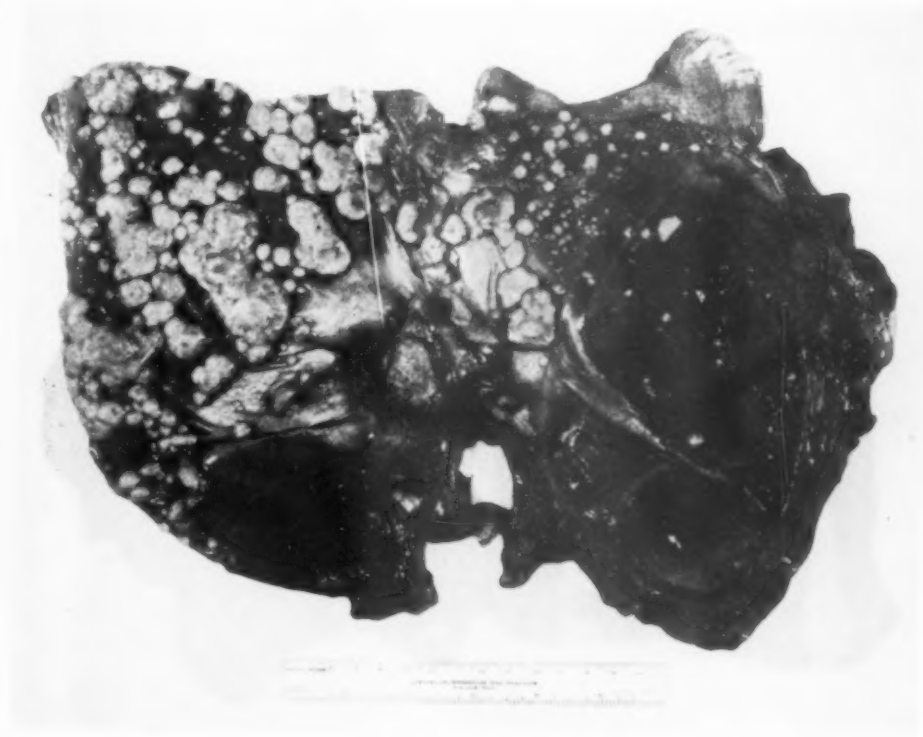


FIG. 1. Secondary adenocarcinoma of diaphragm. From a white man, aged 39 years. The primary tumor was an ulcerating cancer of the pylorus. There were metastases to the liver, both lungs, the retrosternal lymphnodes and the capsule of the spleen. The photograph shows the abdominal surface of the diaphragm invaded by large numbers of flattened tumors.

masses occupying the subserous lymph-channels. From these they ramified, again largely by way of lymphatics, throughout the diaphragmatic muscle (figure 2) grossly appearing as irregularly distributed whitish bands or nodules. While the lymphatics appear to play the chief rôle in the dissemination of carcinoma through the diaphragm, as suggested many years ago by Rajewsky³, two tumors in the present series were probably distributed by way of the blood-stream, namely, the hypernephroma and the spindle cell sarcoma.

Not all of the neoplasms had the gross appearance described above; two of the sarcomas occurred as isolated large roundish masses each the size of a lemon.

The degree of destruction of the diaphragm was generally considerable. The appearance shown in figure 2 is typical of the majority of the cases. It is seen that large areas of the muscle are completely replaced by tumor cells.

TUBERCULOSIS

Tuberculous involvement of the diaphragm is nearly always secondary to some tuberculous focus in adjacent tissues. In the present series the diaphragm showed tuberculous lesions in 35 cases out of a total of 164 diaphragms examined. Curiously, the peritoneal surface was more often affected than the pleural surface, even when the primary focus was in the lung or the pleura. Thus in the case illustrated by figure 3 the abdominal side of the diaphragm was plastered with caseous flat masses, while the pleural surface was smooth and glossy. The primary focus in this case was a tuberculous bronchopneumonia. The gross appearance of the tuberculous lesions was the same as in tuberculosis of serous surfaces in general; there were found isolated miliary and conglomerate tubercles, or more often a true tuberculous serositis. In the later case one or the other surface of the diaphragm was coated with a thick

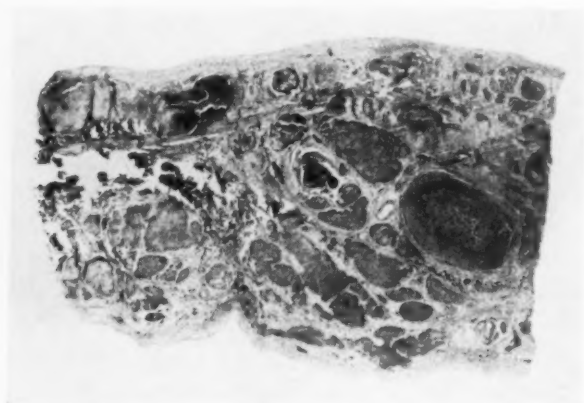


FIG. 2. Metastatic carcinoma of diaphragm, primary in bile-ducts. From a white man, 53 years old. There were metastases to the lungs, mediastinal, retroperitoneal and mesenteric lymphnodes. The photograph (low power) shows the tumor masses largely confined in greatly distended lymphatics. There is extensive replacement of diaphragmatic muscle.

yellow caseous exudate in which no discrete tubercles were found (figure 4). In either form, adhesions to the lung, the liver, stomach or other adjacent organs were commonly observed.

In a considerable number of cases the tuberculous lesions were not confined to the serous surfaces, but tubercles were actually present within the diaphragmatic muscle, not infrequently causing much destruction. It is very probable that the frequency of muscular involvement is due to the rich

lymphatic supply through which the infection is distributed. Indeed of all muscles, the diaphragm probably is most often the site of tuberculous lesions, for tuberculosis of the skeletal muscles is of rare occurrence⁴.

ACUTE INFLAMMATORY REACTIONS AND THEIR CONSEQUENCES

The occurrence of "diaphragmatic pleurisy" and of "diaphragmatic peritonitis" has long been recognized. Inflammation of the muscle of the diaphragm, however, has received very



FIG. 3. Tuberculosis of diaphragm. The peritoneal surface is studded with miliary and conglomerate tubercles between which an exudative reaction may be seen. From a negro, aged 26 years, with primary tuberculosis bronchopneumonia. Histologic examination showed extensive invasion of the muscle.

little attention, although Rohrer⁵, and later Coplin⁶, described in detail the muscular changes generally complicating inflammation of the serous covering. In the present series there were 25 instances of diaphragmitis. Not only was there an inflammation of one

quently a delicate fibrin net could be seen between the muscle fibres. The capillaries were engorged, and the lymph channels prominently distended.

In our series the primary lesion was pneumonia in fifteen cases, peritonitis due to infection of some abdominal

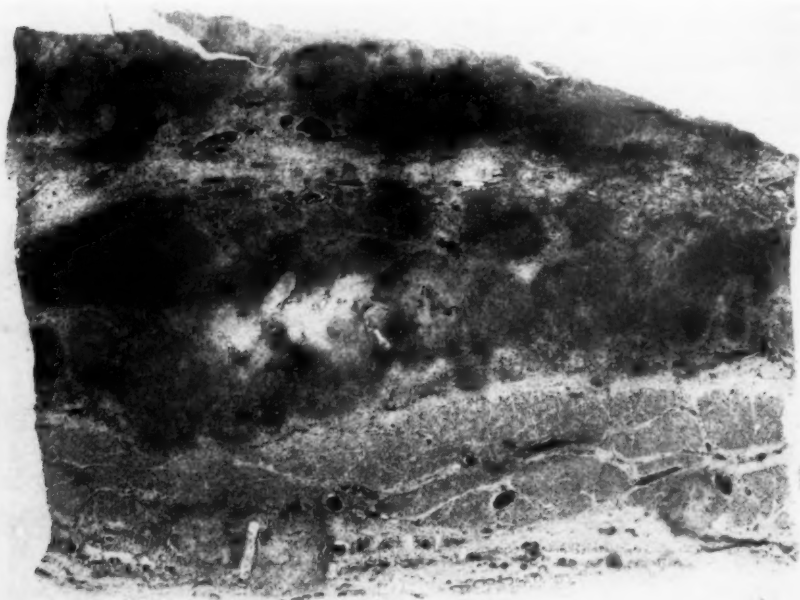


FIG. 4. Tuberculosis of both surfaces of diaphragm. From a negro, 26 years old. The pleural surface is covered with a thick layer of caseous material which merges with a caseous tuberculous (visceral) pleurisy. The photograph shows several large caseous areas within the muscle near the pleural surface. The primary lesion was a typical chronic pulmonary tuberculosis, with terminal miliary tuberculosis.

or both serous surfaces, but in every instance the muscle showed definite changes. In some, these consisted chiefly of degenerative lesions, to be discussed in the next section. In the majority there was present in addition a true myositis. The degenerated muscle fibres were separated by an edematous fluid containing polymorphonuclear leucocytes and occasional mononuclear histocytes. Not infre-

viscus in eight instances; there was one case of general sepsis due to erysipelas and one case of endocarditis. In the latter two cases the infecting agent was probably conveyed to the diaphragm by the blood-stream.

The inflammatory lesions of the diaphragm are probably of very great clinical importance. Rohrer⁵ believed that such lesions occur in every case of pneumonia, an opinion that I am not

inclined to share. I have found many cases of pneumonia without lesions of inflammatory, as contrasted with purely degenerative, character in the diaphragm. Undoubtedly, however, diaphragmitis is of much greater frequency as a complication of pneumonia than is generally recognized. The degeneration of the muscle cells and their separation by inflammatory edema and exudate probably interfere greatly with the efficiency of muscular contraction.

But not only are the acute lesions of significance, but their consequences are likewise of importance. Organization of exudate covering the serous surfaces leads to adhesions, and the repair of the inflammatory foci in the muscle to patches of fibrosis (figure 5).

DEGENERATIONS AND INFILTRATIONS

It has just been stated that various degenerative changes occur in diaphragmatic inflammation. The most common of them are vacuolar degeneration, cloudy swelling, Zenker's hyaline degeneration and fatty degeneration. Of these vacuolar (hydropic) degeneration was most often seen in the cases of diaphragmitis. Here and there muscle cells were swollen and without structural details; there were smaller or larger irregularly shaped vacuoles within the cells. These vacuoles usually contained a faintly eosin-staining fluid (figure 6). Other muscle cells showed cloudy swelling. This was most readily recognized in fresh unfixed and unstained frozen sections

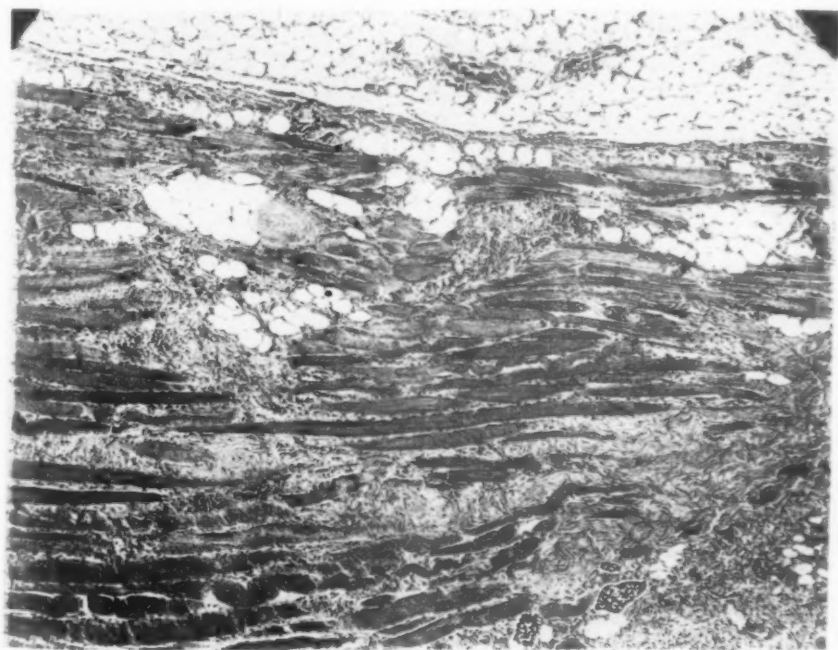


FIG. 5. Subacute diaphragmitis. From a white woman, aged 30 years, who died from widespread lobular pneumonia and staphylococcal abscesses of the lungs. There are scattered small areas of partly organized exudate as well as some older scars. An invasion of fatty-areolar tissue is present.

or teased preparations. The affected cells were large, their striations hazy or entirely lost, the cytoplasm lumpy or granular.

Of the various degenerations of the diaphragm Zenker's hyaline necrosis has received most attention. The subject has been reviewed so recently and so thoroughly by Wells⁷ that no further discussion is here necessary. Wells emphasizes the great frequency with which the diaphragm exhibits this form of degeneration in pneumonia, and indicates the probability that such muscular degeneration may be an important factor in determining respiratory failure in this disease.

Besides these acute degenerations, certain changes of more chronic na-

ture are found not infrequently in the diaphragm. These are the so-called fatty degeneration and fatty infiltration. The former is characterized by the appearance of visible fat droplets within the muscle cells, and by many writers is regarded as an indication of irreversible degeneration. (Figure 7.)

In the present series such fatty degeneration was found most often in cases of severe anemia and in chronic circulatory disturbances, i.e., under the same conditions that fatty degeneration affects the cardiac muscle. Indeed the fatty changes of the diaphragm are very similar to those of the heart; they are patchy in distribution, occurring grossly as yellowish flecks on the cut surface of the reddish-gray diaphrag-

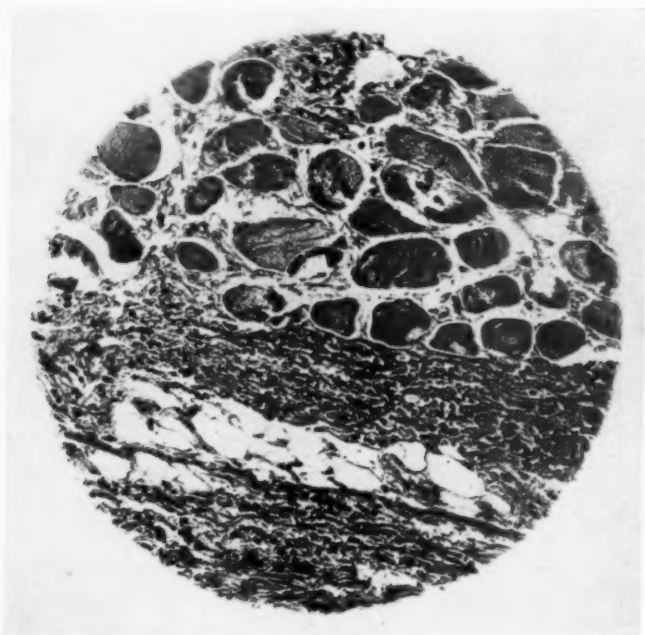


FIG. 6. Vacuolar (hydropic) degeneration of diaphragm. From a white man, aged 52 years, who died from extensive lobular pneumonia. The diaphragmatic pleura is covered with a fibrino-cellular exudate. The muscle cells are swollen, vacuolated, and many have a lumpy or hyaline cytoplasm. The intermuscular tissue is edematous.

matic muscle. Microscopically, the distribution of the affected fibres is extremely irregular; one usually finds markedly degenerated muscle cells bordered by structurally normal fibres. Some fibres contain but traces of visible fat, in others the entire cell is packed with droplets which obscure all details.

Fatty degeneration of the diaphragmatic muscle has been studied by a number of observers^{8,9,10,11}; there is general agreement that of all skeletal muscles the most active, the diaphragm, shows this lesion most often.

Fatty infiltration is a very different process. Under normal conditions the

subserous tissues of the diaphragm contain small amounts of fat, but never in as great a quantity as normally occurs in the subserous areolar tissue of the heart. Under certain conditions there may accumulate a considerable layer of fat, which, when the muscle fibres are atrophic, penetrates between them, thus interrupting their continuity.

DISCUSSION

It is very difficult to evaluate the significance of the lesions described. Certainly it is true that the efficiency of the diaphragm depends above all on the ability of its component muscle fibres to contract properly. In tu-

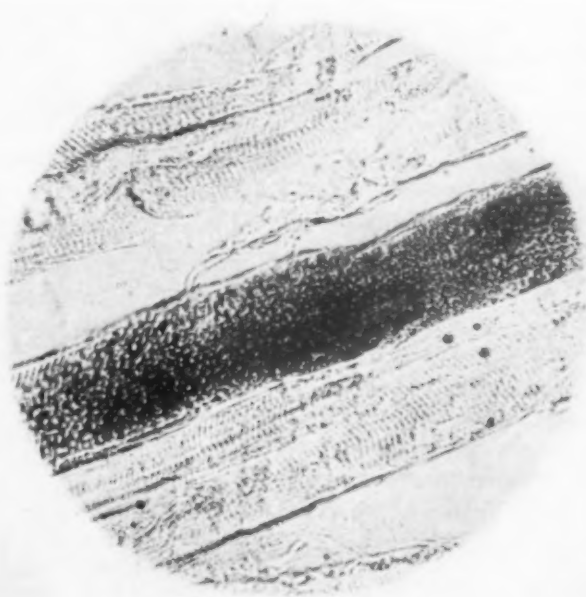


FIG. 7. Fatty degeneration of diaphragm. (Sudan III stain of frozen section.) From a white woman, 62 years old, who had suffered from myocardial disease for several years. She died from decompensation and there was marked dilatation of the heart; the myocardium had a striking mottled yellow to yellow-brown appearance; the tigroid marking was best seen beneath the endocardium of the papillary muscles. Microscopically, there were numerous typically fatty degenerated muscle fibres in the diaphragm, usually lying alongside of structurally normal fibres.

mors, in tuberculosis, in diaphragmitis and in degenerations it may be assumed that the functional powers of the muscle as a whole are considerably impaired, for all of these disease processes are attended by loss of contractile substance. Such impairment of diaphragmatic function may have serious consequences when the respiratory or circulatory mechanism is at fault.* Unfortunately it is very difficult to determine after the death of the patient from clinical records what ef-

fect any diaphragmatic lesion discovered post mortem had on the course of the disease. The true significance of diaphragmatic lesions is yet to be worked out, and this can be done only through experiment and through collaboration of clinician and pathologist in a large series of cases.

*For a discussion of the pathological physiology of the diaphragm reference should be made to the monographs of Eppinger¹² and of Hitzenger¹³, as well as to the writings of Landis¹⁴.

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The Heart and the Diaphragm*†

By I. M. TRACE, M.D., F.A.C.P., *Chicago, Ill.*

WALSHE, writing in 1871 about the clinical importance of the diaphragm, said: "I am persuaded much of their silence depends less on immunity from disease of this musculo-fibrous septum, than upon the rarity with which it is examined post-mortem. Clinical ignorance is the necessary result of this neglect." And even at present the diaphragm hardly gets the clinical considerations its location and functions warrant.

A musculo-fibrous structure, lined with pleuro-pericardial serosa on its upper and peritoneum on its lower surface, it separates the thoracic and abdominal cavities and is in close contact with the cardio-respiratory organs and important abdominal viscera.

Symptomatically sharing the troubles of its neighbors on the north or the comrades on the south, it may be visited by such remote calamities as miliary tuberculosis, trichiniasis, pernicious anemia and scurvy. It is said to undergo degeneration in severe congestive heart failure and marked emphysema (Zahn, Falkenstein, Hitzemberger¹).

The phrenic is its chief motor nerve and its muscle tone is nicely balanced

by an interplay of the sympathetic and parasympathetic forces.

Next to the heart it is the most important muscle in the body (Falkenstein). Structurally and functionally it bears a rough analogy to the heart muscle. It is striated; its contractions are rhythmic, tetanic in character, of long duration, with short intervals of rest. It works unremittingly from the cradle to the grave; but its action is both voluntary and involuntary. Considered at one time the main muscle of respiration, its importance was somewhat dimmed by the surgeon. Unilateral paralysis was found to be no great handicap and even bilateral phrenicotomies were survived. The diaphragm is one of the important muscles of respiration and its chief business is to keep the lower lobes inflated and properly aerated.

The circulatory function of the diaphragm is often lost sight of. The upright posture of man makes the backflow of venous blood difficult. During an inspiratory diaphragmatic contraction the intra-abdominal pressure increases, the intrathoracic becomes negative and the diaphragm acts as a suction pump upon the returning venous blood. The liver, the great reservoir of venous blood, is compressed by the diaphragm, "like a wet mushroom by a grasping hand"

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(Wenckebach), and its blood is forced out into the great veins of the thorax. With each diaphragmatic contraction the intra-abdominal cavity is enlarged and the intracardiac pressure is diminished, with the heart moving caudally, thus facilitating the better filling of the heart chambers.

The pressure within the abdomen varies with inspiration, body positions and distention of the hollow viscera. The intrapulmonary pressure is subject to marked and at times sudden variations. There is a reciprocal and antagonistic relationship between the heart and the diaphragm, and thus between the two cavities, by the diaphragmatic abdominal reflex of Sherrington. A positive hypertonic reflex of the diaphragm is often associated defensively with a negative hypotonic cardiac reflex (dilatation) and a positive hypertonic cardiac reflex is helped by a negative hypotonic diaphragmatic reflex. The diaphragm thus acts as a buffer, protecting the thoracic viscera from excessive intra-abdominal pressure and the abdominal contents from sudden variations in intrapulmonary pressure.

To function efficiently the diaphragm must be unhampered in its movements and maintain an optimum position in the thorax. Its central tendon is at the eighth dorsal spine and it reaches the fourth interspace on the right, the fifth rib on the left anteriorly; posteriorly, the eighth rib on the right and the eighth interspace on the left. Its position is the result of the normal pulmonary pull, muscle tone, and the width of the lower thorax. It varies with the pressure in the thoracic and abdominal cavities and is marked-

ly influenced by posture⁴, being lowest when the person is standing and highest when he is supine; sitting produces no appreciable change in the normal diaphragm.

Even from this fragmentary anatomico-physiologic survey it is quite evident that the diaphragm is a friendly intermediary and helpful ally, and it is hardly surprising to find it parading at times in the clinical garb of its neighbors, especially the heart.

Young adults and children not infrequently have pain in the lower axillary regions on walking or running. When the pain is on the left side the heart comes under suspicion. If the heart is found normal, as it usually is, the pain is due to spasm of the diaphragm.

A fit of laughter is likely to provoke similar discomfort as the following case will illustrate.

A Gypsy of forty-five, complained of pain in the precordium, radiating to the shoulder, of three days' duration. The pain was severe and was aggravated by exertion, by loud and fast talking. The cardio-circulatory apparatus was normal. Further questioning brought out that while in a speak-easy, swapping stories with his comrades, an especially good one caused a fit of laughter and the pain appeared shortly after. The fluoroscope showed jerky movements of the left diaphragm. Strapping relieved the pain immediately.

In effusive pericarditis the diaphragm may become inflamed by contiguity. Nausea, vomiting and hiccoughing may dominate the picture and obscure the diagnosis. When with the diaphragmitis there is also a phrenic involvement, pain in the shoulder and dysphagia may be so severe that the mere sight of water or

food will cause pain, the so-called hydrophobic type of an effusive pericarditis⁶. Swelling and tenderness of the liver may come on before fluid can be demonstrated in the pericardial sac clinically and be quite puzzling. It is due to an embarrassment of the vena cava inferior by the faulty movements of the right diaphragm.

The sequence of events may be reversed. A left sided diaphragmatic lesion may cause severe heart pain.

A man of twenty-four was awakened at two in the morning with severe anginal pain radiating to the shoulder, which required morphia. The pain recurred two or three times daily for about three weeks, the patient running a septic temperature. The chest showed nothing abnormal. Fluoroscopy was likewise negative, the left diaphragmatic outline being clear, regular in outline and its lateral half moving freely with some haziness in the left costo-phrenic angle. The needle obtained 5 c.c. of slightly cloudy fluid. Three weeks after the onset, edema appeared in the epigastrium, slight bulging soon following. Incision revealed pus in the left subdiaphragmatic space close to its central portion. With drainage the fever subsided, the pain disappeared and the recovery was speedy. The cause of the abscess remained obscure.

When a chronic pericarditis works through the diaphragm and involves the capsule of the liver, Pick's pseudo-cirrhosis is likely to result. Its classical diaphragmatic phenomena of epigastric systolic retraction during inspiration and Broadbent's systolic tug posteriorly are familiar to every clinician. It is not generally known that occasionally an unaccountable right pleural effusion⁷ may be its earliest manifestation, more so when associated with an enlarged liver. The compromised right diaphragm apparently interferes with the action of the

right heart or compresses the supra-diaphragmatic portion of the vena cava inferior (Hanot⁸).

Milder forms of an adherent pericardium often entirely escape clinical detection. Demonstrating the immobility of the apex by percussion, while often diagnostically helpful, is not always possible in women, in the obese, and in the emphysematous. The fluoroscope with the patient in the left lateral position will diagnose⁷ the condition with certainty and ease. Normally the heart moves away from the dependent left chest on deep inspiration; this movement is most marked in the lower left cardiac contour. With an adherent pericardium this movement is slight or entirely absent. With the patient in the erect position there may be present an upward systolic tug⁸ of the left diaphragm.

Dyspnea may at times be the outstanding symptom of a chronic diaphragmitis. It is a good clinical rule to suspect the diaphragm, when the dyspnea is out of all proportion to the findings in the chest.

Not infrequently following an effusive pleurisy of some duration, dyspnea appears upon exertion. Re-examination shows marked dullness with diminished breath sounds, ectasia is absent, even retraction of the intercostal spaces may be present. Fluid is still suspected, but the tap is dry. The fluoroscope shows no fluid, but haziness and immobility of the diaphragm. Needling, as suggested by the Japanese, stimulates the lazy diaphragm to increase its respiratory excursions and to keep the lungs inflated. Pryor describes severe dyspnea in pneumoconiosis involving the diaphragm. The

patient is pale; the heart is small and tube-like; the apex beat is feeble and the heart tone distant. When fibroid phthisis invades the diaphragm, dyspnea may become quite troublesome.

Sudden and severe dyspnea is likely to come on following operations on the upper abdomen or injury to the chest wall. The clinician suspects an acute pulmonary atelectasis; the physical findings may, and the x-ray does, diagnose the condition. While it is conceded that bronchial obstruction by viscid secretion is the main factor⁹ in the pathogenesis of a massive pulmonary collapse, the defensive splinting of the thoracic wall and of the diaphragm, already handicapped by the supine posture, play no small contributory part by abolishing or diminishing the diaphragmatic excursion and interfering with the efficient respiratory dilatation of the lungs and their ability to expel the bronchial secretion¹⁰. Yandell Henderson¹¹ suggested that carbon dioxide be given at the end of the anesthesia to induce deep respirations and properly inflate the lungs.

Eventration or relaxation of the diaphragm, whether congenital or acquired, is usually left sided. The raised left diaphragm does not compress the pulmonary base but lifts and moves the heart to the right. Most often symptomless, it will occasionally give rise to a cardio-diaphragmatic syndrome of precordial distress, dyspnea and angina-like pain upon a full stomach or intestinal distention in the gonadal and adipose dystrophies and in the myocardiopathies³.

The findings of basal tympany with diminished breath sounds, the apex in the fourth interspace, with the trachea

displaced to the right, while suggestive, are nearly always overlooked and the diagnosis is made by the fluoroscope. The left diaphragm is high, its outline is regular but faint, it may show paradoxical movements and easily moves upward when pressure is exerted upon the abdomen.

Any one past forty with a girth of generous proportions is well acquainted with the discomfort in the chest, fullness of the head and the turgescence of the face when, on a full stomach, he is called upon to lace a shoe. The increased abdominal pressure moves the diaphragm up and temporarily embarrasses the circulation. Flatulence frequently provokes extrasystoles, and that angina pectoris is more prone to appear upon a full stomach is a well known clinical fact. One wonders if the frequency of acute coronary thrombosis, masked as an acute indigestion, at the height of a generous banquet, is not due to embarrassed filling of already sclerosed coronaries by a distended stomach pressing up the diaphragm against a diseased heart.

Indeed, any factor favoring an increased intra-abdominal pressure is likely to call forth circulatory difficulties, especially in the obese, in those of sthenic habitus, and in the gravidæ. Dietlen⁴ maintains that in the obese with dyspnea the poor or absent mobility of the diaphragm brings about deficient pulmonary ventilation and venous disturbances in the thoracic and abdominal cavities.

It is not uncommon to see men of sthenic habitus in the fourth or fifth decade, short of neck, broad of chest, red of face, with tense muscular abdominal walls, complain of some short-

ness of breath and precordial distress upon exertion. The thickened arteries, the aortic configuration of the heart with the apex displaced to the left, and short systolic murmurs heard best or appearing only during expiration, logically enough point to the heart, but the fluoroscope shows a high diaphragm and a squatty left heart silhouette well buried in the diaphragmatic shadow. The electrocardiogram shows left axis deviation. In the obese the third lead may show complete inversion¹².

It is hard to ascertain in these cases just what part the heart plays in the production of the symptoms. It is difficult to absolve it from all guilt, since Pearce³ has shown experimentally that the abdomino-visceral reflex responsible for the clinical syndrome of dyspnea and cardiac distress does not effect the normal heart, but only when the myocardium is injured.

About the seventh month of pregnancy the enlarging uterus widens the lower thorax¹³, flattens and pushes up the diaphragm. The apex is raised and rotated to the left, basal râles and even murmurs may appear. (Dietlen¹).

A para two of twenty-six, eight months pregnant, complained of dyspnea upon exertion and edema of the ankles. There was no history of rheumatic infections or previous cardiac discomfort. The heart was apparently out to the left with a short systolic mitral murmur not transmitted. Left axis deviation was present in the electrocardiogram. It was interpreted as a normal heart temporarily mechanically embarrassed by the increased intra-abdominal pressure. Six weeks after delivery the heart and the electrocardiogram were normal and the patient in the best of health.

Another gravida of thirty with a very large abdomen had dyspnea and annoying extrasystoles. Delivery relieved her of both.

Mackenzie¹³ explains the cardiac discomfort in the gravidae by the embarrassment of the right heart by the lessened respiratory movements. The latter obviously are hampered by the high and flattened diaphragm. Normal hearts withstand this temporary load quite well. In diseased hearts, with the right ventricle already considerably overtaxed as in mitral stenosis, the increased load may lead to serious cardiac failure or acute suffocative pulmonary edema.

The following case is very instructive:

A para three, with a mitral stenosis, when eight months pregnant developed some cough and dyspnea upon exertion. When almost at term, during an obstetric examination and while flat on her back, she became cyanotic, coughed incessantly, and an alarming pulmonary edema quickly supervened. Only heroic treatment saved the patient. Rest in bed with digitalis carried her to term, when she was delivered by Dr. Louis Rudolph quite uneventfully in a semi-sitting position.

The abnormally high diaphragm is not the only source of diaphragmatic dysfunction¹. The low diaphragm, when pronounced, is productive of a goodly share of chronic invalidism. Its owner is nearly always thin and pale, with a long and narrow chest and a protuberant ptotic abdomen. The extremities are cold and the blood and pulse pressure are low. The abdominal organs are palpable. Nearly always the victims of numerous poorly defined digestive complaints, they are not infrequently subjected to many unnecessary and repeated abdominal operations. Frequently circulatory disturbances assert themselves; dizziness, dyspnea, palpitation, and fatigue upon exertion bring them to the physician. These

patients present all the symptoms of an effort syndrome: the heart is small, the pulse weak and the muscles flabby. The fluoroscopic examination shows a narrow heart hanging suspended like a drop from the large blood vessels. The diaphragm is low, with poor respiratory mobility, and is definitely separated from the cardiac shadow. The poor filling of the cardiac chambers causes a relative arterial anemia with the subjective sense of exhaustion and the suspended heart, lacking its diaphragmatic support, is likely to produce such bizarre findings as a paradoxical pulse or even a tracheal tug. (Wenckebach¹.) A well applied abdominal support quickly brings relief. Prolonged rest in bed,

hyperalimentation, aided by insulin, as suggested by Falta, often improve the general condition remarkably.

The physician, who in physical diagnosis of the lungs takes into consideration the depth and shape of the thorax, the thickness of the parietes, the position of the heart and the mobility of the diaphragm, may profitably be on the alert in evaluating cardiac symptoms also, in connection with two important factors: the position and the mobility of the diaphragm. He will be rewarded by a better understanding of the mechanism of some symptoms and by fewer diagnostic errors, and the patient will profit by more intelligently applied therapeutic procedures.

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Malignancy in the Lung: Including Eight Primary Carcinomas With Autopsy Findings*†

By HENRY MONROE MOSES, A.M., M.D., F.A.C.P., Brooklyn, N. Y.

ROBERT J. Graves, of Dublin, who so clearly described exophthalmic goiter that the condition is still called Graves' Disease, in a clinical lecture¹ on the Practice of Medicine, delivered nearly ninety years ago, wrote "I shall conclude this lecture with the description of a singular and uncommon disease of the lungs. Rare diseases should not be looked upon as mere matters of curiosity, but should be attentively studied with the view of enabling us to recognize the true nature of similar cases when they again occur." He continues, "The diagnosis of encephaloid tumors of the lungs was, a few years ago, completely impossible; but, I trust, that ere long we may be enabled to arrive at some degree of certainty, even in this difficult and obscure branch of thoracic pathology."

Morgagni², (1682-1772) who laid the foundation of pathological anatomy, was probably the first to publish the results of several autopsies on lungs that might be diagnosed as cancerous, and were so interpreted by him.

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†Read at a Meeting of the Brooklyn Society of Internal Medicine, November 28, 1930.

It is probable that the first of the cases which he published as cancer of the lungs was really an example of primary lung tumor. In this case, he describes the disease of a man sixty years old, which was accompanied by cough and copious expectoration of a yellowish, rather crude material, rarely, but then distinctly stained by streaks of blood. At autopsy, the lung was found extremely hard with adhesions to the pleura and mediastina, and nothing else but an "ulcus cancrorum" in the right lung³.

Adler⁴, in his masterful study of Primary Malignant Growths in the Lungs and Bronchi, states that "lung tumors were absolutely unknown in ancient and medieval medicine until the time of Morgagni." This statement is no doubt true from all our known medical literature concerning medical conditions of ancient and medieval times. It seems impossible to the writer that metastatic growths from malignancies in other organs never occurred or were never found in the lungs of those afflicted. It is hoped that at some later date accounts of such new growths in the lungs will be found in the writings of physicians of the ancient times. The belief that

primary neoplasms of the lungs are among the rarest forms of disease has persisted for centuries, and it is only within the last few years that this belief is becoming changed, because of the comparatively great number of tumors of the lung being found and studied. For several years there has been a growing belief that intrathoracic cancers are increasing in frequency. This belief is being confirmed more and more by recent reliable statistics. In a study of the incidence of primary carcinoma in the lung, Rosahn⁴ concludes that "the post-mortem incidence of primary carcinoma in the lung is steadily increasing, and this increase is real and absolute." Whatever may be the explanation, primary carcinoma in the lung is more common now than formerly. The cause of this greater frequency of occurrence is not known. This increase was commented upon by Adler³ who published his study in 1912, and who did not suggest any reason for it. Davidson⁵, of London, in a study of

cancer in the lung, published in 1930, states that "it seems reasonable to suppose that for an explanation of the increase of primary carcinoma in the respiratory tract, we must look to some factor which, since the period of the War has begun to operate in greater degree, and which, through the production of specific tissue irritation, may account for this hitherto unusual localization of malignant disease in such individuals as are especially susceptible."

In a large, general hospital such as the Kings County Hospital, with an average daily census of 1710 patients, ample opportunities are presented for the study of malignant conditions in the lungs, whether primary or secondary. It has been the privilege of the writer to review the appearance of malignant diseases at the Kings County Hospital during the decade from 1920 to 1930, and in addition to include eleven months of 1930. The following figures are presented of malignant tumors, Kings County Hospital.

TABLE I
Evidence of Malignant Tumors and of Metastases

<i>Year</i>	<i>Patients</i>	<i>Tumors</i>	<i>Metastases</i> <i>To</i>	<i>Metastases</i> <i>General</i>
			<i>Other Organs</i>	
1920	10698	232	37	—
1921	13931	279	13	—
1922	16200	298	19	—
1923	18131	312	42	—
1924	19594	396	68	13
1925	19969	437	85	6
1926	19715	373	75	4
1927	21236	406	96	10
1928	23719	355	48	11
1929	24948	334	66	15
	188241	3422	549	50
1930 to Nov. 1st	24288	245		

TABLE II
Metastases to the Respiratory System

Year	Lung	Pleura	Larynx	Trachea
1920	—	—	—	—
1921	4	—	—	—
1922	6	—	—	—
1923	2	1	—	—
1924	5	—	1	—
1925	3	1	—	1
1926	3	—	1	—
1927	5	—	1	—
1928	6	1	1	—
1929	5	2	1	—
	—	—	—	—
1930	39	5	5	1
to				
Nov. 1st.	10	—	—	—

TABLE III
Malignant Tumors of the Respiratory System

Year	Lung	Larynx	Pleura	Epiglottis
1920	2	3	—	—
1921	1	3	—	—
1922	6	10	—	—
1923	—	5	1	—
1924	9	7	—	1
1925	7	5	—	1
1926	6	5	—	—
1927	3	4	—	—
1928	7	4	—	1
1929	6	12	2	—
	—	—	—	—
1930	47	58	3	3
to				
Nov. 1st.	7	12	—	1

Patients with malignant tumors in the lungs may be divided into three general classes for diagnosis:

First, those upon whom a diagnosis can be made only on post-mortem examination, because of the absence of any general or pulmonary symptoms, except weakness and emaciation; or because the patient is seen only when moribund, and the usual physical findings of malignant tumor in the lungs are masked by other conditions.

Second, those upon whom a diagnosis can be made easily by reason of evidence of tumor growth in other parts of the body, in addition to the pulmonary findings.

Third, those upon whom a diagnosis of new growth in the lungs can be made because of the history, the course of the disease, the physical findings and the absence of tumor growth in other organs.

The presence of a malignant tumor in the lung is not always an easy matter of diagnosis, and unless the growth causes enough discomfort for the patient to seek a physician, the condition may not be discovered during life.

CASE REPORTS

Case I. On November 22, 1927, M. J., a woman 82 years old, was admitted to Kings County Hospital with a cellulitis of the scalp. Ten days before admission, the pa-

tient had fallen down stairs and had received a scalp wound which became infected. The cellulitis was properly cared for, but the patient's general condition was poor, apparently due to her eighty-two years of age. Three days before her death, or seventeen days after her admission to the hospital, the patient was drowsy, became comatose and died. The belief was that she had a generalized atherosclerosis and died from kidney failure. However, we were fortunate enough to have permission for a post-mortem examination. The histological findings of interest to us at the present time are as follows: The lungs showed emphysema, chronic fibroid pneumonia, congestion and edema and an area of epidermoid carcinoma. The liver showed chronic passive congestion. The kidneys showed a chronic glomerulonephritis. Here we have a primary carcinoma of the lung, in a patient who apparently had no pulmonary symptoms.

Case II. Another patient, No. 59553-30, autopsy No. 8734-30, a man, age 52 years, was admitted to Kings County Hospital and died forty-eight hours later. He was extremely pale, was struggling for air, and had been drinking large quantities of whiskey for more than a month. He was a chronic alcoholic. His condition was critical on admission. His blood pressure was 80/60. He became unconscious shortly after entering the hospital but could be aroused. His red blood cells were 1,060,000 and his hemoglobin was 35 per cent. A history obtained from his family reported a gastric hemorrhage and bloody stools about one month before admission. He complained of pain in the abdomen. The patient did not show emaciation. During his short stay in the hospital, he was restless and fighting for air. There were many coarse, moist râles throughout both lungs. The object of treatment of this patient was to support and stimulate him over the emergency. However, he died forty-eight hours after admission. Our feeling was that he had a severe anemia, a chronic alcoholism, with an alcoholic wet brain. A post-mortem examination was permitted, of which the points of interest to us now are: "The right lung shows infarcted areas at the base, which are well circumscribed, and adjacent to this is

found a cavity from which pus escapes. At about the centre of the middle lobe, there is a tumor-like mass, five and one-half centimeters in diameter. This mass is firm, nodular and white in color. The pleural surface of the left lung is thickened and rough. On section, a frothy fluid can be expressed from the cut surfaces. The ribs and vertebrae have tumor-like growths. The diaphragm, also, shows raised nodular masses which are hard. There is no gross pathology of the trachea or esophagus. The mucosa of the stomach near the pyloric end and the duodenum show denuded areas suggestive of old ulcer formation; the remainder of the gastro-intestinal tract is grossly normal. Histologically the patient showed acute purulent bronchitis, pulmonary abscess, confluent broncho-pneumonia, metastatic lymphosarcoma in the lung, lymphosarcoma of the peribronchial glands, metastatic lymphosarcoma of the bones and chronic ulcer of the duodenum. Here we have another patient upon whom the diagnosis of malignant tumor in the lung could not be made because of his condition on admission to the hospital. Ewing,⁶ in his book on Neoplastic Diseases, states that "frequently these new growths are discovered only at autopsy." Adler³ states "one form that occurs occasionally is that of a single nodule, usually quite small surrounded perhaps by a few minute malignant nodules deeply buried in the lung tissue of one lobe, producing only very slight or possibly no symptoms during life, and as a rule, discovered by mere accident at autopsy."

There are some patients upon whom the diagnosis of malignant tumor in the lung is not difficult to make.

Case III. A young man, No. 56734-30, a laborer, 21 years old, was admitted to Kings County Hospital, August 13, 1930, with the following complaints: Weakness, pain in the chest and in the abdomen, and loss of thirty pounds weight in six months. On January 10, 1930, the patient was operated upon for hernia complicated by an undescended testicle, and a varicocele operation was performed. On July 27, 1930, at Kings County Hospital, his left testicle was removed. Following this operation, he had pain almost contin-

nously in the abdomen and in the flanks. One week before admission, on August 13th, pain appeared in the lower part of the chest on both sides. Upon auscultation, the patient had numerous râles throughout the left lower lobe, and râles below the scapula on the right side. There was a lump at the upper angle of the scar of the operation on the testicle.

A résumé of the radiographic reports follows: Numerous well defined nodular metastases are strewn throughout both lungs; these nodules varying from approximately 1 to 4 cm. in diameter, being definitely spherical, borders well defined; these are more commonly situated near the periphery. Osseous system examination fails to reveal any evidence of abnormality of texture of the bones of the skull, extremities or trunk. Conclusions: Nodular type of pulmonary metastases, probably the result of sarcomatous infiltration. (See figure 1.)

This man died October 26, 1930, seventy-four days after admission to the hospital and ninety-one days after removal of the testicle. The diagnosis with this patient was not difficult, as the pathological report from the section of removed testicle is as follows: "The section shows testicle and epididymis. The testicular portion shows no marked change from the normal. The epididymis, however, presents a neoplasm composed of varying types of cells, some being large and round, some showing eccentric nuclei and rather horse-shoe shaped, and still others showing cells not unlike those known as the reticulum cells of lymph nodes. Hyperchromatism is quite a marked feature. There are numerous areas of necrosis. The neoplasm is definitely histoid in morphology. The diagnosis of the tumor is polymorphocellular sarcoma." With this young man, it was not difficult to make a diagnosis of metastatic sarcoma in the lungs.

Case IV. Another type of patient, No. 24877-29, Autopsy No. 7796-29, admitted to the Kings County Hospital, was a woman forty-seven years old, who complained of pain in the chest, weakness, loss of weight and dyspnea. This patient died seven days after admission to the hospital. She had had a breast amputated six months previously for carcinoma. The autopsy revealed metastases

to the lungs, heart, liver, adrenals and mesentery. A diagnosis, before death, of metastatic carcinoma in the lung was not difficult.

Although we know many times that we have a metastatic tumor in the lungs from a primary malignant growth elsewhere in the body, the classification of the type of tumor is not always as easy a matter as in the two preceding patients.

Case V. A man, No. 5989-28, Autopsy No. 7291-28, forty-six years old, was admitted to Kings County Hospital complaining of pain localized in the right chest and upper abdomen about the costal margin, and included between the anterior and posterior axillary lines. This pain had persisted for two weeks and was described as if needles were sticking into him. The patient stated that at the onset of this attack, he had vomited for five days. There was no blood in the vomited material. On admission, the patient did not appear acutely ill, but did show signs of emaciation. A slight cough was present. He had signs of fluid in the right pleural cavity. There was marked epigastric and upper rectus rigidity. Later a bloody fluid was removed from the right pleural cavity. The conditions considered as possible were chronic pulmonary tuberculosis, pleural effusion, malignancy in the lung, chronic gall-bladder disease, peptic ulcer and malignancy in the epigastric area. This patient died thirty-one days after admission to the hospital.

A résumé of the radiographic reports follows: Examination of the gastro-intestinal tract fails to reveal any evidence of organic lesion of the stomach, duodenum or intestines. There is moderate enlargement of the liver. Examination of the lungs, eleven days later, reveals a large effusion of the right pleural cavity, with displacement of the mediastinal contents to the left, and a localized area of incomplete consolidation at the level of the third left interspace. The only diagnosis warranted on the radiograph of the lungs is a localized area of consolidation and a large, pleural effusion. The new growth element can only be defi-

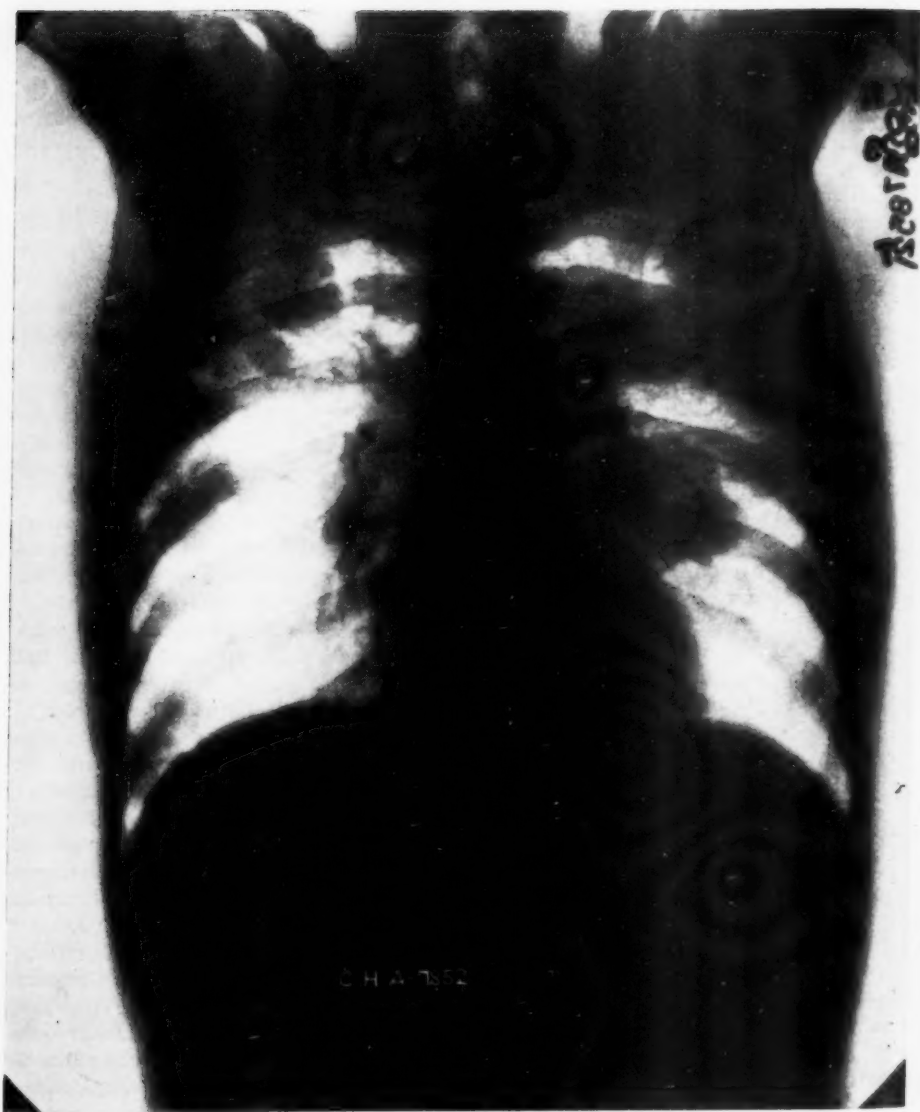


FIG. 1. Case III. Metastatic tumors in the lung. Numerous well defined areas of infiltration of the parenchyma of various size, spherical in shape, occupy chiefly the upper lobes particularly about the level of the first and second interspaces anteriorly. This is a nodular metastatic neoplastic infiltration from a primary growth in the testicle, diagnosed histologically as embryonal carcinoma.



FIG. 2. Case IX. A large, spherical area of non-aeration, approximately 10 cm. (film measurement) in diameter, occupies the posterior portion of the upper right lobe. There is no evidence of displacement of the mediastinal contents. There is partial absence of the lateral portion of the second rib, probably due to pressure erosion. This is pulmonary neoplasm of the primary type in the right upper lobe.

nately determined by removal of fluid and a re-examination:

The histological findings at autopsy were:

Brain: Metastatic hypernephroma.

Pericardium: Metastatic hypernephroma.

Lungs: Congestion, edema, anthracosis and metastatic hypernephroma.

Right Kidney: Hypernephroma.

Peritoneum: Metastatic hypernephroma.

Vena Cava: Metastatic hypernephroma.

Case VI. Another patient of this type was a woman, No. 58893-30, Autopsy No. 8704-30, 39 years old, admitted to Kings County Hospital with abnormal pulmonary symptoms, as well as general signs of severe disease. This patient died seven days after admission. A post-mortem examination was made which yielded the following information:

Lungs: Metastatic teratoma.

Liver: Metastatic teratoma.

Adrenals: Metastatic teratoma.

Kidneys: Acute suppurative pyelonephritis.

Urinary Bladder: Acute gangrenous cystitis.

Spinal Dura mater and Posterior Nerve

Roots of Upper Lumbar Cord: Metastatic teratoma.

Ovary: Primary malignant teratoma.

It is not difficult to realize from the histories, that each individual patient with a new growth in the lung can present an interesting problem in diagnosis.

Hamman⁷, of Baltimore, writes "In the lungs, tumor growth may cause cavities, bronchiectasis, erosion of blood vessels, sometimes with fatal hemorrhages, and it may be accompanied by a bronchopneumonia, empyema, abscess or gangrene." He adds, "a small lung tumor that gives no local symptoms may cause widespread metastases; any organ or tissue may harbor metastases, but lymph glands, liver, bones and kidneys are most often invaded." Because of the

variety of the modes of expression of these new growths, the diagnosis of malignant tumor of the lung is not always an easy diagnosis to make.

Case VII. A colored man, 46 years old, was admitted to Kings County Hospital and died twenty-five days later. He complained of pain in the right chest, anteriorly, of four months duration; he had a productive cough for six months, with occasionally blood tinged sputum; he had lost thirty-two pounds in weight in five months; he had a marked dyspnea, and complained of extreme weakness. We have presented here the usual symptoms of malignancy of the lung, with the report of a negative Wassermann reaction, and numerous sputum reports negative for tubercle bacilli. He showed signs of serious trouble in the right upper lobe. The radiological report stated: This is a lobar type of lung tumor in the right upper lobe with degeneration and cavitation.

This patient was presented for bronchoscopy. We received the following comment: Owing to considerable pus and mucus coming from the right bronchus, and also due to the presence of edema of the same bronchus, the examination was not completed. Two weeks after admission, the patient expectorated a red, bloody sputum. Eight days later, he developed a pneumonia in the right lung and died in three days. Clinically this is a patient with a primary carcinoma of the lung, but in the absence of a post-mortem examination, it is impossible to call it primary.

Case VIII. A man, No. 19143-26, forty-six years old, was admitted to the Kings County Hospital and died fifty-two days later. This patient stated that for the past nine months he had been unable to work because he had not felt well. There were present as complaints: Cough, pain in the chest on the right side, loss of twenty pounds in weight in six months, general weakness, night sweats and anorexia. The patient appeared acutely ill. His temperature was 101.6°, his pulse was 90 per minute, his respirations were 20 per minute. His breath was foul, his mouth contained many carious teeth, the uvula and pharynx were

injected. His chest was of the emphysematous type. There was dullness on percussion and tubular breathing over the right upper lobe. A few scattered râles were heard over both apices. The conditions found suggested a new growth in the right upper lobe. The radiographic report stated that the picture was suggestive of new growth in the upper lobe, right side. Lipiodol injection revealed none of the mixture in the right upper lobe, probably the result of occlusion of the right bronchus, consequent to a new growth. The report of a bronchoscopic examination showed that the trachea was found fixed, and pushed towards the left. On the right lateral wall in the region of the fourth or fifth tracheal ring there was a small, irregular granulation-like mass about two millimeters in diameter. Because of the fixation of the trachea, entrance into the right main bronchus was difficult. At the entrance of the upper lobe bronchus, an irregular mass was encountered and a section was removed for examination. Microscopic report of the section taken was epidermoid carcinoma.

This patient's urine was normal. Numerous sputum examinations were negative for the tubercle bacillus. His blood Wassermann was negative. His blood chemistry showed the following: Urea, 40 mg. per 100 c.c.; creatinin, 1.2 mg. per 100 c.c.; sugar 105 mg. per 100 c.c.

His blood count showed: Red blood cells, 3,360,000; hemoglobin, 70 per cent; white blood cells, 15,100; polymorphonuclears, 80 per cent; small mononuclears, 15 per cent; large mononuclears, 2 per cent; transitionals, 3 per cent; morphology, normal.

The following interesting comment is made on the history. This is a case of malignant tumor of the lung, carcinoma. The question of primary or secondary growth must be left to further study by necropsy. Unfortunately it was impossible to obtain a post-mortem examination of this patient.

Fortunately with the patient whose history I now present, we were granted permission for a post-mortem examination.

Case IX. A man, No. 55210-30, Autopsy No. 8668-30, forty-six years old, was admitted to the writer's service at Kings County Hospital complaining of severe, paroxysmal pain in the right chest for seven weeks, cough productive of a whitish sputum, which was blood tinged on two occasions eight weeks and four weeks before admission, loss of twenty-five pounds in weight in six weeks, cyanosis, marked dyspnea upon slight exertion, anorexia since the onset of pain. This patient had always enjoyed good health except for an attack of influenza during the epidemic in 1918—twelve years previously. At the time of his admission, the patient was in no acute distress, and did not appear acutely ill. There was diminished tactile fremitus over the upper right lobe to the fourth rib. Dullness on percussion was present over this area, with cavernous breathing and increased whispered voice transmission. There were no râles on cough over this area. Tenderness was present along the course of the fourth rib, which was roughened in the anterior axillary line. While in the hospital, this patient showed mental symptoms, suggestive of metastases to the brain. The blood Wassermann was negative. Repeated examinations of the sputum were negative for the tubercle bacillus. The urine at the time the temperature was 101° showed a trace of albumin, many finely granular and hyaline casts and some leucocytes. The blood examination showed red blood cells, 3,468,000; white blood cells, 16,900; polymorphonuclear cells, 75 per cent; small mononuclears, 21 per cent; large mononuclears, 1 per cent; transitionals, 2 per cent; eosinophiles, 1 per cent; hemoglobin, 70 per cent.

A résumé of the radiographic reports states: There is complete consolidation of the upper portion of the right lung, the lower level of which is noted at the level of the fourth rib anteriorly; the lower border of this consolidated area is convex downward; the remainder of this lung and the left present no evidence of pathological changes. Conclusions—the findings are indicative of pulmonary neoplasm of the upper lobe, right.

This patient died nineteen days after admission.

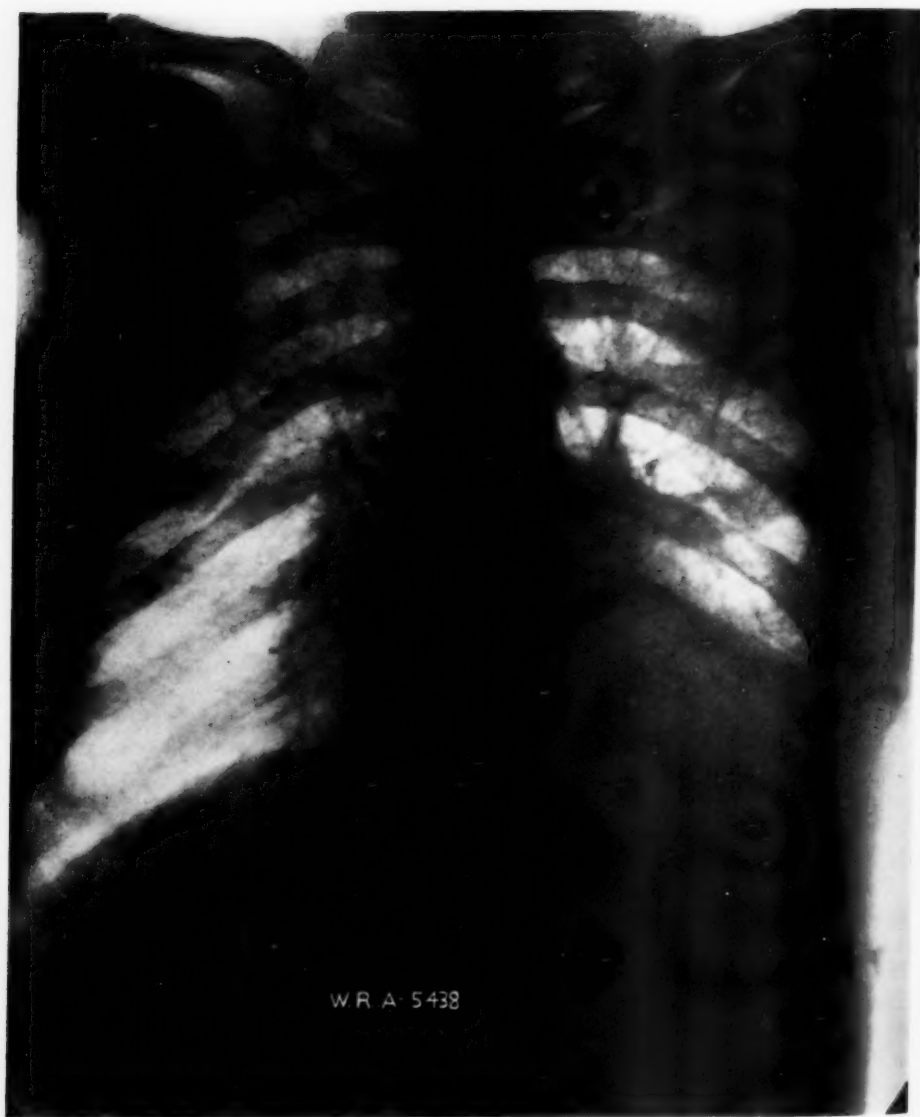


FIG. 3. Case X. Primary carcinoma of the lower lobe of left lung. Consolidation extends almost to the periphery laterally.

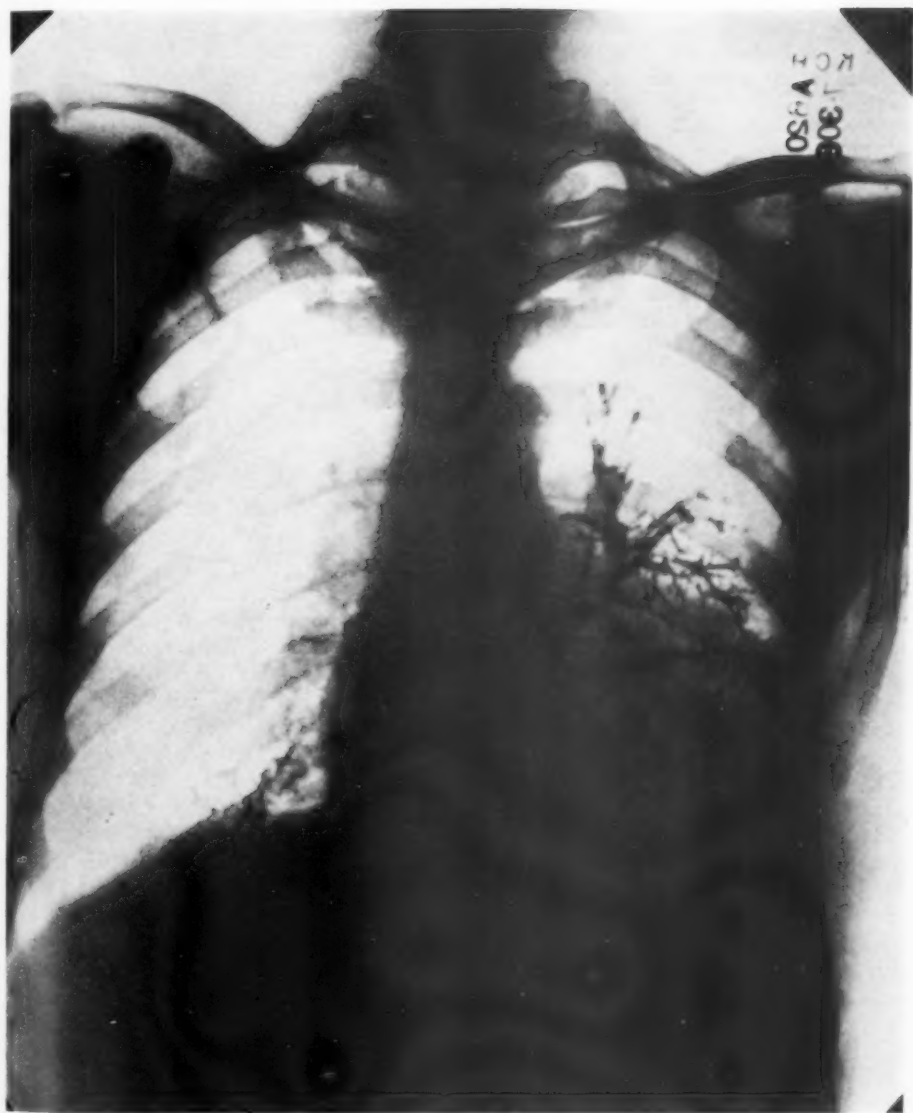


FIG. 4. Case X. Primary carcinoma of the lung. Bronchography. Complete obstruction of the lower left bronchus supplying the inner half of the lower lobe.

The post-mortem findings were: Carcinoma of the lung, primary, right side; congestion of the liver and the spleen; cloudy swelling of the kidneys; congestion and edema of the lungs.

Peritoneal Cavity: No free fluid, no adhesions.

Right Lung: Densely adherent to the parietal wall, especially the upper lobe; stripped away with difficulty. There was marked erosion of the 2nd, 3rd and 4th ribs in the mid-axillary line. On section, the upper lobe was found to be filled with a grayish firm tumor mass, in the central portion of which there was a large cavity filled with a reddish cloudy fluid. The lower lobes were dark red and congested, but showed no evidence of tumor.

Left Lung: There was some congestion and edema at the base; no enlargement of the mediastinal glands.

Pericardium: No free fluid, no adhesions.

Histological examination of the lungs showed the presence of a tumor composed of interlacing islands of squamous cells, and here and there occasional attempts at pearl formation. The histologic picture was one of typical epidermoid or squamous-celled carcinoma; and in view of the fact that no other primary focus was observed at autopsy, it is probable that this was an example of primary epidermoid carcinoma of lung, possibly metaplastic. (See figure 2.)

Case X. Another patient, on the writer's service at the Kings County Hospital, admitted June 18, 1930, was a man, Case No. 64670-30, Autopsy No. 8831-30, forty-five years old. The patient had noticed for the past year weakness, loss of weight and cough. He had pain in the left chest and shoulder for the past three months, also extreme dyspnea. Physical examination was suggestive of new growth in the left lower lobe, with possibly pleural effusion. No fluid was ever obtained from the pleural cavity. On admission, his blood counts did not show a secondary anemia; his leucocytes were 10,150. An anemia developed later. His blood chemistry was normal. His urine showed a low specific gravity, 1012; a faint trace of albumin; a few hyaline and finely granular casts. The patient remained

in the hospital 152 days before death, expectorated much bloody sputum, had much pain in left lower chest and lost much weight. A résumé of the radiographic report, states: Examination of June 19th, the day following his admission, reveals an irregular area of consolidation occupying the inner and posterior portions of the lower left lobe. No evidence of other pulmonary or pleural pathological changes noted. Approximately one month later, this area of consolidation of the lower lobe, left, is noted to be increased, extending almost to the lateral periphery. (See figure 3.)

One week later, bronchography was done by the passive method, at which time there was noted a complete obstruction of the lower bronchus, left, supplying the inner half of the lower lobe (figures 4 and 4A). The occlusion of this bronchus was complete. The remainder of the bronchi extending from the lower main stem were noted to be of moderate size, usual contour and distribution.

Diagnosis: New growth, bronchogenic type, of the lower lobe, left.

A bronchoscopic examination made July 31st, 1930, revealed a hard mass obstructing the left main bronchus in the region of the left lower lobe. A specimen of this mass was obtained for examination. A second bronchoscopic examination was made two weeks later, with the findings similar to those of the first examination. The histological report of the biopsy specimen, examined by Doctor Hala, was as follows: The section is one of new growth composed of irregular islands of epithelial cells of the types which are encountered in the two lower layers of the epidermis. The remainder of the section consists of a fibrous stroma with here and there small mucous glands of normal appearance. Diagnosis: Epidermoid carcinoma.

The post-mortem examination revealed: Emaciation, carcinoma of the lung with involvement of the left bronchus and lower six ribs and dorsal vertebrae, cystic adenoma of the thyroid gland, cloudy swelling of the myocardium, congestion and edema of the lungs, chronic splenitis, moderate passive congestion of the liver, acute nephrosis, atheroma of the aorta, cysts of the adrenals,

adipositas of the pancreas, bronchopneumonia, bilateral pleuritis.

At the lower left bronchus, there was found a tumor-like mass with involvement of the left lower lobe throughout. The thyroid was somewhat smaller than normal; on section, the architecture was somewhat distorted and had a shiny appearance. The centre of each lobe was cystic. The lungs were dark gray in color. The pleurae were thickened and adherent throughout both cavities. In the lower left portion of the chest, a tumor-like mass about the size of a grapefruit was found, involving the ribs and vertebrae. These were somewhat soft, friable and undergoing rarefaction. The lungs had a shotty feel throughout. The left lower lobe was entirely made up of tumor and was adherent to the diaphragm. In areas, it was firm, and on section, presented a white, gristly appearance. In other portions of the lung, the appearance was ragged and moth-eaten. The right lung exuded a frothy fluid from the cut surfaces.

The histological data were as follows:

Bronchus. The mucosa was absent, and replaced by a tumor consisting of connective tissue stroma and incorporating numerous and irregular islands of epidermal cells.

Left Lung: The section showed the presence of a neoplasm which was similar in architecture to that observed in the wall of the bronchus, consisting of numerous islands of epidermal neoplastic cells. There was but little attempt at ultimate differentiation in the tumor cells. In only one area could there be observed an attempt to form an epithelial pearl.

Diaphragm: Attached to the diaphragm was a rather large nodule of tumor which in structure resembled that already described in the bronchus.

Aorta: Atherosclerosis. The adventitia of the aorta was invaded by nests of epidermal neoplastic cells.

This is evidently a case of primary carcinoma of the lung, originating in the left bronchus. The tumor is definitely of epidermoid structure.

The following history is of interest because it was read at the meeting of

the Brooklyn Society of Internal Medicine on November 28, 1930, as that of a patient with a carcinoma of the lung which we believed to be primary in the lung. This patient died November 28, 1930, and an autopsy was permitted which proved that the carcinoma was primary in the lung.

Case XI. A man, Case No. 65352-30, Autopsy No. 8846-30, 50 years old, was admitted to Kings County Hospital July 28, 1930, and died November 28, 1930, after one hundred and twenty-three days in the hospital. He complained of pain in the left chest, cough with expectoration, which was never bloody, weakness, loss of weight and anorexia. These symptoms had been more noticeable during six weeks before admission, although the patient had given up his business, six months previously.

Examination showed the presence of a new growth in the left lung. No masses were found in the abdomen. There were no enlarged glands present. A rectal examination showed no prostatic enlargement. On November 1st, the patient developed a consolidation of the right upper lobe. During the latter part of the patient's stay in the hospital, his expectoration became more profuse and more foul. Three days before death, the following note was made: "The patient coughs considerably and raises much sputum; he has some change in his voice sound. There is a sigh with each breath, which has a laryngeal quality. He is suffering considerable pain, and has been getting progressively worse." Hemoptysis was never present during his stay in the hospital. Repeated examinations of his sputum were negative for the tubercle bacillus. His blood Wassermann was negative. His urine showed the following:

Specific gravity, 1012; faint trace of albumin; occasional hyaline casts. Blood Chemistry:—Urea, 20 mg. per 100 c.c. of blood; creatinin, 1.1 mg. per 100 c.c.; sugar, 106 mg. per 100 c.c.

His blood on admission was: Red blood cells, 4,448,000; white blood cells, 5,750; polymorphonuclear cells, 68 per cent;



FIG. 4A. Case X. Bronchography. Primary carcinoma of lower left bronchus. Oblique position.



FIG. 5. Case X. A bronchogenic tumor whose origin is just at the bronchial bifurcation (see arrow). At A are seen secondary tumor masses in the pulmonary parenchyma.

hemoglobin, 80 per cent; morphology, normal.

A résumé of the radiographic reports states: There is a slight decrease of aeration of practically the entire upper lobe, left, with a moderately large mass of irregular contour at the left hilus. In the posterior portion of the lower lobe is seen a horizontal fluid level, which is indicative of a partially filled abscess cavity. Examination of the osseous system at this time revealed no tumor growths in the bones. Examination three months later revealed no further decrease of aeration of the upper lobe, left, and a partial decrease in the lower lobe; the mass at the hilus has increased in size and in its outer portion is an irregular area of re-aeration indicative of partial destruction (degeneration) of this process. Conclusions: A primary new growth of bronchogenic type with partial obstruction to the aeration of the left upper lobe and infection with abscess cavitation in the left lower lobe as described, and probable degeneration of the neoplastic mass in the upper lobe.

A report of the bronchoscopic examination follows: Direct laryngeal examination reveals a complete paralysis of the left vocal cord with partial involvement and limitation of the right vocal cord. Examination of the bronchi reveals an extensive growth involving the left main bronchus, including the corina and extending to the right bronchus (posterior left lateral aspect). A specimen of the tumor was taken for microscopic study. The report upon this specimen is that "this section shows a portion of tumor growth which is composed of numerous islands of squamous epithelial cells. Mitotic figures are present. Diagnosis: epidermoid carcinoma."

Upon the death of the patient, permission was obtained to perform a post-mortem examination, which revealed:

Primary carcinoma of the left lung with involvement of the lower six ribs on the left side and the corresponding vertebrae; acute nephrosis; vascular nephritis; chronic myocarditis; congestion and edema of the lungs; bilateral pleuritis; abscess of the lung, left; moderate passive congestion of the liver; acute splenitis; general arteriosclerosis; adiposis of the pancreas; emaciation.

The body was that of an elderly male about fifty-five years old, rigor present; lividity absent; emaciated and dehydrated, with the supra- and infra-clavicular depressions marked.

Upon removal of the sternum marked bilateral pleuritic adhesions were found. The omentum was attached in the gall-bladder region beneath the liver. The left lung adhered to the posterior wall of the thorax, especially in the region of the lower six ribs and corresponding vertebrae. The lung was freed and a solid tumor mass was found involving the lower lobe in its posterior aspect, and in the anterior aspect, an abscess cavity was noted. The corresponding ribs and vertebrae showed rarefaction of bone. The right lung was rather shotty on palpation. The pleura was thickened, and on section, a small amount of frothy fluid could be expressed. No tumor could be noted in the right lung, but the peribronchial lymph glands were markedly enlarged, and also, extending down from the bifurcation of the bronchus, a tumor-like mass was noted having a fungus-like appearance. The entire left lung showed consolidation except at the upper portion of the lower lobe which contained an abscess cavity about the size of a lemon. Dissection of the bronchus of the left side show neoplastic infiltration which began about 0.75 cm. above the bifurcation and continued down about 2.5 cm. into the left bronchus. At the terminus of the bronchus on the left side, was an abscess cavity. The lung on section showed this circumscribed cavity, and also a tumor-like mass involving the upper and lower lobes, with thickening of the pleura.

Histological data:—

Heart: Marked adiposis; cloudy swelling of myocardium.

Lungs: Epidermoid carcinoma. The tumor cells, in general, are squamous in morphology and are surrounded by fibroblastic tissue. The section incorporates part of the bronchus which latter shows evidently the primary focus.

Liver: Cloudy swelling, moderate chronic passive congestion.

Spleen: Congestion and edema.

Adrenals: Cloudy swelling, congestion and edema of medullae.

Pancreas: Moderate adiposis.

Kidneys: Cloudy swelling.

Aorta: Calcification of media.

Cause of Death: Primary carcinoma of the lung, with involvement of the lower six ribs and corresponding vertebrae.

On January 24, 1931, a short time before the preceding section of this paper was prepared, a patient, M. N., a woman 52 years old was admitted to Kings County Hospital with the following complaints:—Cough of four months' duration, with slight expectoration, not bloody; pain in the left chest; loss of weight, fourteen pounds in four months; dyspnea, of two months' duration, increasing in severity; no night sweats.

One month before admission, the patient developed what she called a "fresh cold," which persisted. For the past two months, the patient slept only on the left side because of increase in cough and dyspnea in any other position. On admission, the patient was not emaciated, did not appear acutely ill, was not suffering severe pain, but had a marked dyspnea.

Physical examination revealed the signs of an effusion in the left pleural cavity and, possibly because of the recent review of the subject, the resident physician made the additional diagnosis of malignancy in the lung.

Thoracentesis was performed twice; five days after admission, 1500 c.c. of a clear, serous fluid was withdrawn, and eleven days after admission 1250 c.c. of a dark amber fluid. Both fluids under the microscope showed many red blood cells and were transudates.

Examination of the blood on admission showed:

Red blood cells, 3,808,000; white blood cells, 12,200; polymorphonuclear cells, 70%; small mononuclear cells, 25%; large mononuclear cells, 3%; transitional cells, 1%; eosinophilic cells, 1%; hemoglobin, 80%.

Blood Chemistry:—Urea, 30 mg. per 100 c.c. of blood; creatinin, 1.2 mg. per 100 c.c.; sugar, 145 mg. per 100 c.c.

Examination of the urine showed no abnormalities. Sputum examination was negative for the tubercle bacillus. Blood Wassermann was negative. Six days after ad-

mission, blood streaked sputum was present and there was a sharp rise in temperature. During the stay in the hospital, the temperature varied between 99.8° and 104.4° and never became normal. The dyspnea increased in severity, cyanosis was marked and the patient showed an increasing heart impairment. On the seventeenth day in the hospital, an erysipelas developed on the left side of the head and face, the temperature rose to 103°, the pulse to 124, and the respiration became 32. Signs of a bronchopneumonia were present. Radiographic reports taken on admission and later were "massive effusion of the pleural cavity". Twenty-one days after admission, the patient died, apparently from cardiac involvement.

The findings on post-mortem examination were unusually instructive. They revealed:

Congestion and edema of the lungs; bronchopneumonia; primary bronchogenic carcinoma on the left side; bilateral pleuritis; chronic myocarditis; atheroma of the aorta; acute and chronic pericarditis; passive congestion of the liver; septic spleen; chronic vascular nephritis; degenerated adrenal; chronic fibrotic oophoritis.

Marked bilateral pleural adhesions were found. In the left thoracic cavity about 100 c.c. of cloudy, gray, thin fluid was present, and a fresh, fibrinous plastic exudate surrounded the entire lung and upper surface of the diaphragm. The right cavity showed a similar plastic exudate and a moderate amount of transudate fluid also. The pericardium was adherent to the left lung and occupied about twice the normal space in the mediastinum. The lungs weighed 1800 gms.

The left lung was of a grayish white color. A firm, tumor-like mass had invaded the lower portion of the upper lobe, the major portion of the lower lobe and in an area about the diameter of a silver dollar had extended into the visceral pleura. The trachea and bronchi which were dissected out with the lungs, were incised and inspected and the tumor-like growth found to have begun, apparently, about one-half inch below the bifurcation, in the left bronchus, showing a line of demarcation which was pale, anemic and in marked con-



FIG. 6. Case X. A primary carcinoma of the lung of the epidermoid type with its origin just at the tracheal bifurcation, (see figure 5). At the right is seen the margin of a normal bronchiole.



FIG. 7. Case XI. Primary bronchogenic carcinoma of left lung.

trast to the normal tissue. The left lung on section, presented a pale, grayish growth, indurated in character and occupying the portions of the lobes above mentioned. The peribronchial lymph nodes were also involved, being enlarged, firm and fibrous.

The right lung was dark gray in color with no apparent metastases. On section, there was a patchy consolidation in the lower lobe showing grayish, granular areas. A frothy fluid could be expressed from the other lobes. The pericardium was thickened and adherent to the left lung, also to the epicardial surface giving the appearance of "bread and butter," the *cor villorum* or *hirsutum*, especially over the left ventricle. In the region of the right ventricle, old fibrinous strands were present. The visceral layer of the pericardium was hemorrhagic and injected.

The heart was markedly enlarged, weighing 600 gms. The ventricular walls were thinned out and of light brown color. On section, fibrosis was present in the musculature. The mitral leaflets were somewhat thickened along their free borders; the aorta showed raised atheromatous plaques; the coronaries were narrowed.

The cause of death was: Primary bronchogenic carcinoma of the left lung.

Histological examination confirmed the findings of primary carcinoma of the lung, together with bronchopneumonia, acute seropurulent epicarditis, chronic fibroblastic pericarditis, acute seropurulent pericarditis, facial erysipelas.

It is a privilege to present here for the first time, the histories of five patients with primary carcinoma of the lung proven by autopsy. These five, together with the three reported in detail by the writer⁸, in 1925, make a series of eight cases of primary carcinoma of the lung at the Kings County Hospital since February, 1924; three in 1924, and one in 1927, and the four last mentioned within the past six months. We feel that a number diagnosed as carcinoma of the lung, upon which no autopsies were permitted,

were primary growths in the lung; the four patients whose histories have just been given were diagnosed as carcinoma before death and the primary condition was proven when post-mortem examination was allowed.

In making a diagnosis, the following steps are taken: The history, the physical findings, the course of the disease, and as at the time of Graves' lecture, the gross findings of tumor at autopsy. To these findings have been added:

- (1) The fluoroscopic examination and the roentgen ray picture;
- (2) The bronchoscopic examination and the microscopic examination of the specimen obtained during life;
- (3) The histological findings at autopsy.

The use of the bronchoscope has been of inestimable value as an adjunct in diagnosing these malignant conditions.

"The value of bronchoscopy in diagnosis is primarily dependent on data obtained by direct visual inspection. It must be remembered, however, that in a diagnosis of pulmonary disease, the entire lungs are not open to inspection. Only the larger bronchi can be examined. The minute branches cannot be inspected by any endoscopic means. However, secretion can be observed coming from the orifices of the small branches and uncontaminated specimens of this can be removed for bacteriological study. Positive findings are of the utmost value. Bronchoscopy is indicated when there is a diagnostic question remaining after physical examination, radiographic studies and laboratory investigations have been carried out⁹."

In reviewing eighty-one histories of patients at the Kings County Hospital, presenting evidence of malignant tumors in the lung, the writer found pa-

tients who may be classified as follows:

Eight with primary carcinoma in the lung.

Thirty-five with what is believed to be carcinoma in the lung, without autopsy, and not metastatic from other organs.

Twenty with metastatic carcinoma in the lung.

Ten with metastatic lymphosarcoma.

Six with metastatic sarcoma.

One with metastatic hypernephroma.

One with metastatic teratoma.

Primary sarcoma in the lung is rare. Carcinoma is the commonest tumor in the lung, whether primary or secondary. These secondary growths may occur by direct extension from contiguous carcinomata, or as metastases from distant tumors. Pleural effusion is usually the first evidence of direct invasion from the breast or the stomach. Of carcinomata that metastasize to the lung, breast and kidney tumors are clinically the most important. These metastases are frequently small, and even though they may be numerous, they may cause few pulmonary symptoms, and are usually overlooked clinically. Occasionally miliary carcinomatosis of the lung occurs. The association of obscure or unusual pulmonary symptoms and signs with one or more nodules in the bones is peculiarly characteristic of hypernephroma, although it may be present in sarcoma.

From the histological viewpoint, three types of pulmonary carcinoma are recognized, arising respectively from the bronchial epithelium, the

bronchial mucous glands, and the alveolar epithelium. In other words, they may be bronchogenic or parenchymal.

Carcinoma arising from the bronchial epithelium often causes bronchial obstruction and bronchiectatic cavities; it seldom causes a diffuse tumor of the lung.

Carcinoma arising from the mucous glands begins in the large bronchi. A number of small growths have been described of glandular structure with mucous secretion beginning in the walls of the bronchi, and covered by intact bronchial epithelium. These typical mucous gland tumors infiltrate the bronchial wall, often causing bronchial obstruction. As the tumor spreads by direct growth and by metastasis, the characteristic gross and histological picture may become obscured. The secretion of abundant mucus is a very characteristic feature of mucous gland growths, although it is not restricted to them.

Carcinoma arising from the alveolar epithelium produces infiltrating masses which often spread rapidly, involving a lobe or larger areas, and somewhat resemble organizing pneumonic consolidation. At times, instead of a diffuse growth, multiple nodular tumors are formed.

Secondary sarcoma of the lung is less common than secondary carcinoma, although melanotic sarcoma and sarcoma of the bone almost always metastasize to the lungs. Pulmonary lympho-sarcoma must always be secondary to tumors arising in lymph glands or in the thymus.

"General weakness is a frequent complaint, often an initial one, and tends to increase as the disease progresses, but wast-

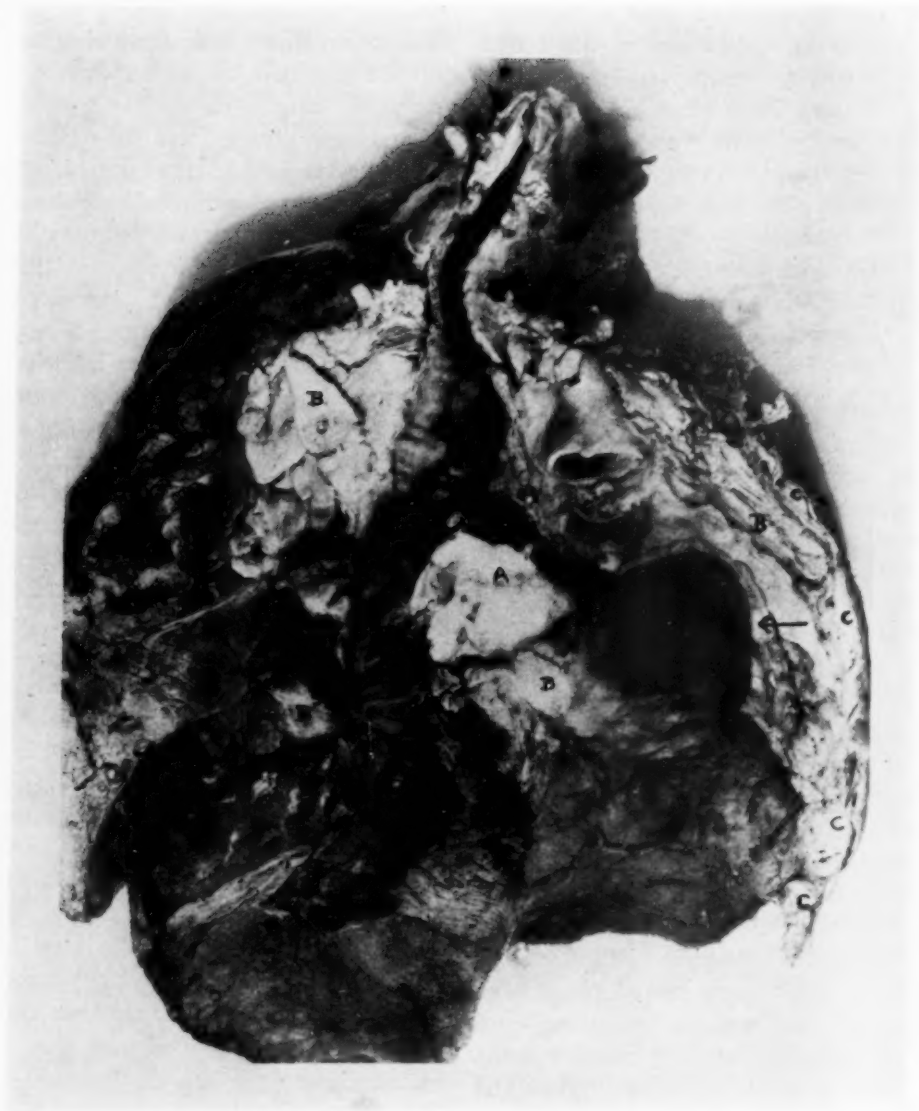


FIG. 8. Case XI. Primary carcinoma of the lung. This neoplasm is bronchogenic in origin and its focus can be seen readily at the bifurcation of the trachea just above A. The mucosa of both bronchi is infiltrated for some distance below the bifurcation and at A the tumor has advanced into and through the bronchial wall. Secondary nodules are exhibited at B. The arrow points to a large bronchiectatic cavity. There is considerable thickening and invasion of the visceral pleura at C.



FIG. 9. Case XI. Primary carcinoma of the lung. This section shows an epidermoid type of growth in the lung parenchyma. There is considerable fibroblastic stroma. The primary growth in this case is illustrated in figure 8.

ing is by no means a constant occurrence in malignancy of the lung. In some patients, however, the onset of manifest symptoms is slow and insidious. In a number of patients, the first serious manifestation of disease occurs with comparative suddenness. The patient may seek the physician

(1) primarily on account of hemoptysis, the cause of which has either not been determined, or has been thought erroneously to be tuberculosis of the lungs;

(2) because of evidences of pleurisy with or without effusion;

(3) those whose history and physical examination suggest the presence of a localized infection within the chest;

(4) those suffering from grave disability and showing the more obvious phenomena which characterize the later stages of intrathoracic malignant disease".⁵

In regard to the presence of pleurisy, we feel that the commonest cause of pleurisy in the young adult is tuberculosis. We also feel that we must always keep in mind that the occurrence of an unexplained pleurisy, especially of a pleurisy with effusion, in a patient of middle age or later, should suggest the question of the presence of new growth in the lung or mediastinum. If the effusion is bloody, it may be regarded as almost pathognomonic of malignant disease in the lung or pleura. The presence of tubercle bacilli in the sputum does not exclude malignancy of the lung, which may co-exist with pulmonary tuberculosis. A malignant tumor may be present in the lung of a patient having syphilis, and one has to make a differential diagnosis between gumma of the lung and a non-syphilitic tumor.

No brief description of the physical signs can be given. These must differ according to the type of the disease, the site of the tumor, the extent of lung involved, and the presence or ab-

sence of effusion in the pleural cavity.

As we may see from the histories of these patients, the commonest signs and symptoms are:

Cough with or without expectoration, which, if present, may be bloody.

Hemoptysis,

Dyspnea—very severe in some cases,

Pain—which may be steady or paroxysmal,

Cyanosis,

Weakness,

Emaciation—which is not always present,

Gastric symptoms—which may be present but are not common,

Fever—which may be present in moderate degree, due to secondary illness.

What may we consider the prognosis in these patients with malignancy of the lungs? The general rule in all malignancy—"the earlier in life that the growth appears, the more malignant it will be," seems at present to be our answer.

The mode of death may vary in different individuals. There may be a gradual general failure. Death may result from sudden, large hemorrhage; this is considered rare. The patient may have a hemiplegia due to metastasis lodging in one of the cerebral vessels and causing embolism. He may lapse into coma due to a growth in the brain tissue; more often the coma is due to a toxic state, with a general septic absorption. There may be sudden and distressing dyspnea with death.

What should be our feelings concerning the treatment and the results

of treatment in these severe conditions? When one considers that the treatment of malignancy seems now as hopeless as did the treatment of pernicious anemia when many of us began the study of medicine, we should be hopeful of developing a cure in malignancy. How wonderfully, indeed, has the prognosis in pernicious anemia been changed by the use of liver and defatted stomach in treatment^{10,11}. Surely, we must be encouraged, also, by the advance in the methods of treatment of many of the scourges of the world, such as the use of quinine as a specific in malaria, the vaccine for small-pox, antitoxin for diphtheria, anti-tetanic serum in the prevention of tetanus, typhoid and paratyphoid vaccine in the prevention of typhoid and paratyphoid fevers, and meningococcic serum in the treatment of meningococcic meningitis. Something must and will be found to combat successfully every malignancy wherever it may be found in the body. The surgeons feel that surgery may be of benefit where it is possible to discover the condition early. Electrical treatment, and possibly radium, may be the means by which this seemingly hopeless problem will be solved. The cure may be accomplished before the cause of malignancy is discovered.

I wish to acknowledge here my appreciation to my colleagues at the Kings County Hospital in all departments of the Hospital for the cordial co-operation accorded to me in reviewing this work. Doctor Rendich, Director of the Radiographic Service, has kindly read the radiographic pictures; and Doctor Hala, Director of the Pathological Service, has kindly translated the pathological slides; the Record Room Service has been invaluable in correlating this review.

Without this co-operation, it would have been impossible to have completed this agreeable task.

SUMMARY

A study of eighty-one patients with malignant tumors in the lung presented:—

Eight with primary carcinoma in the lung, confirmed by autopsy;

Thirty-five believed to be carcinoma in the lung; the diagnosis having been made on the history, physical examination, radiographic findings and bronchoscopy with biopsy specimen, but without autopsy;

Twenty with metastatic carcinoma in the lung from a primary focus elsewhere;

Ten with metastatic lymphosarcoma in the lung;

Six with metastatic sarcoma in the lung;

One with metastatic hypernephroma in the lung;

One with metastatic teratoma in the lung;

It has been possible to demonstrate and illustrate in this paper every step in arriving at the diagnosis of primary carcinoma in the lung.

Of the eight primary carcinomas in the lung, all were found to be unilateral, with four involving the right lung and four involving the left lung. The symptoms presented by these eighty-one patients varied according to the stage of the disease, the type of tumor, the site of the tumor, the amount of lung tissue involved, and the presence or absence of effusion in the pleural cavity. The commonest symptoms were cough, with or without expectoration, which, if present, was usually bloody at some period of the

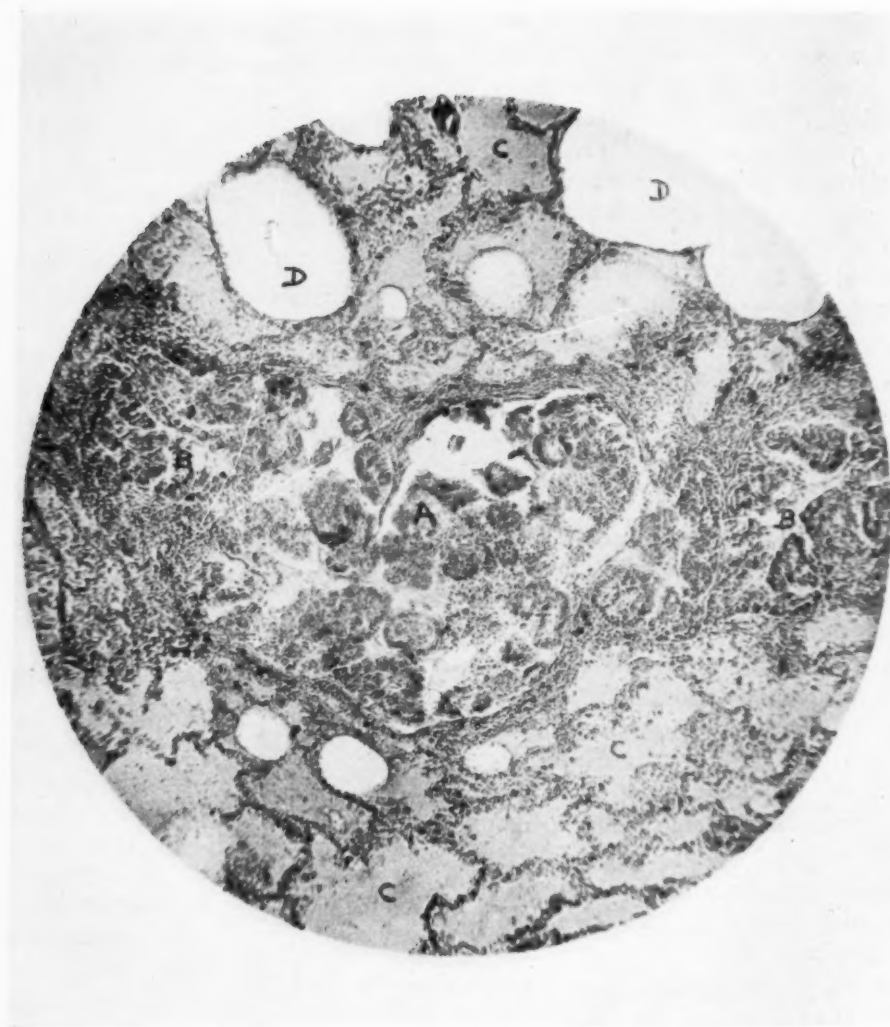


FIG. 10. Case XI. Primary carcinoma of the lung. This tumor is definitely adenomatous in architecture as is well shown at A. This is a type which is bronchogenic in origin and undoubtedly derived from the submucosal glands of a bronchus. In the lower part of A, the cylindric epithelium is well demonstrated. The growth has a tendency to be papillated at B. Edematous alveoli are found at C, and compensatory emphysema at D.

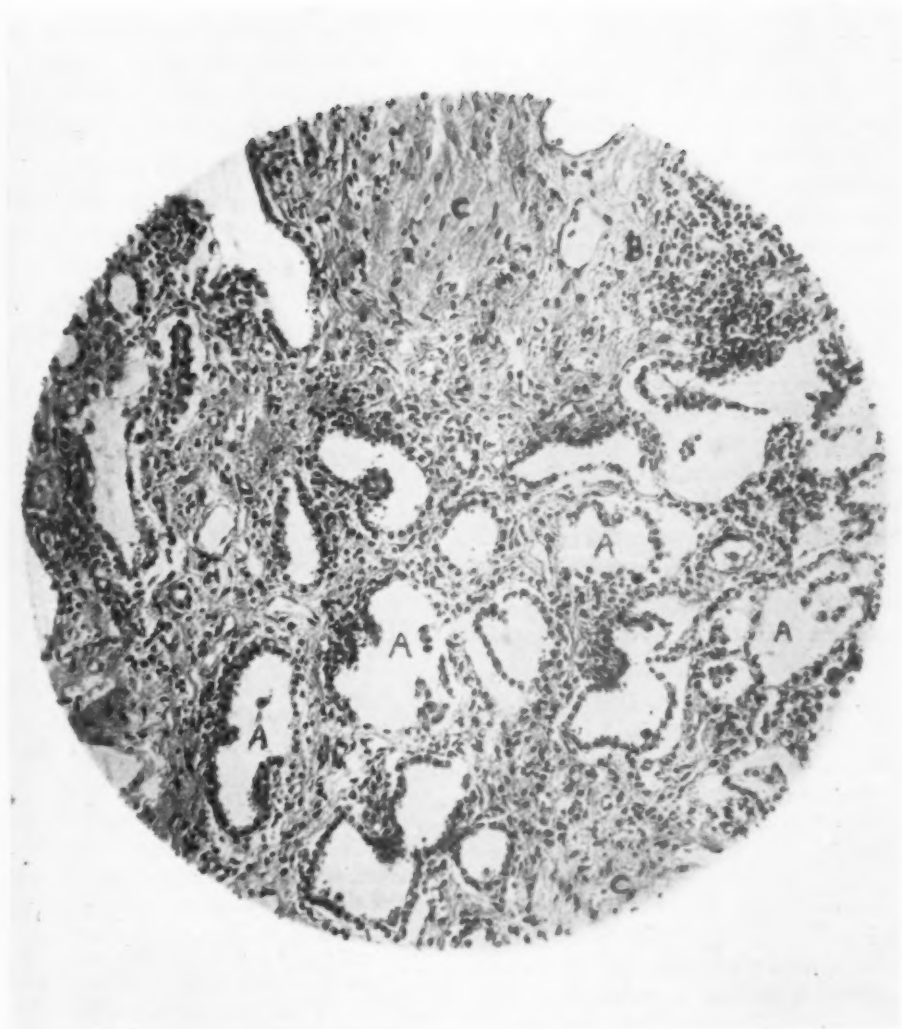


FIG. 11. Adenomatoid changes in the lung. This section is from a patient having pulmonary syphilis and illustrates the possibility of neoplasia secondary to a luetic lesion. A group of gland-like spaces is seen at A. They are lined by cubical cells. At B is a small miliary gumma, while fibroblastic tissue (an example of the productive inflammation unfailingly observed in lues) can be seen at C.

disease; dyspnea; pain; cyanosis; weakness; emaciation. Hemoptysis was present in those patients having blood vessels involved in the tumor, with ulceration. Fever may be present in the early stages in the presence of a pneumonitis which is usually diagnosed as an atypical pneumonia which does not resolve completely; in the later stages, fever is present because of an inflammatory process in and about the tumor. Abstracts of the histories of eleven patients are given, illustrating these conditions. The post-mortem findings are reported with nine of these histories.

Secondary growths in the lung show an advanced condition of malignancy in the body, and although electric treatment may ameliorate the symptoms and prolong the patient's life, not a great amount of benefit is believed to result from the present treatment of these secondary conditions.

In primary cancer of the lung, in order to diagnose the condition earlier than is usually done, it is necessary that we concentrate our attention (1) upon those patients who complain of persistent cough without demonstrable causes; (2) upon those patients who expectorate bloody sputum at intervals; with no tubercle bacillus in the sputum; (3) upon those patients who complain of general weakness, loss of weight, and do not react to the usual methods of treatment. The value of post-mortem examinations is demonstrated here, and our constant effort should be to obtain permission for more of these examinations. We must be hopeful in the not too distant future for cure of these malignant conditions, as the slight benefit from electrotherapy may be the forerunner of methods to inhibit and stop the destruction of life by these "outlaw" growths.

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The Dietetic Treatment of Tuberculosis*†

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IN a previous article the writer has discussed this subject from the administrative standpoint. This discussion will include a broad outline of early history of food supply and diets and its effect upon early medical opinion in the attempt to show how these factors have influenced man's ideas concerning the importance of diet in tuberculosis. While there is still a wide difference of opinion as to the most valuable diet in tuberculosis, an attempt will be made to outline a sane and reasonable basis for the diet used at Glen Lake Sanatorium. Although it is realized that an improvement in nutrition alone may have no effect on the tuberculous lesion, we still believe that every effort should be made to improve the nutrition of the patient, so that his resistance to infection in general may be increased and his sense of well-being improved.

The importance of diet in the treatment of tuberculosis has as its background all of the weight of economic and medical history. Until comparatively recent times the common man has suffered from an unsatisfied hunger. For instance, in the times of the Greeks and the Romans a three pound

mullet cost the equivalent of seventy to eighty dollars in today's money, and at one time Domitian ordered a special session of the Senate to determine the best way to cook a turbot. Surely ancient man loved his food and its palatability was of great importance to him. In the time of Queen Elizabeth only about one-half of the common men had fresh meat as often as once a week and the other half never tasted it at all, and in the time of Louis XV a pound of sugar cost sixty to eighty francs. Therefore, about all that was available for the poor man was bread, peas, soup, bark of trees and certain raw vegetables which are now recognized as very important articles of diet but which were formerly scorned by the wealthy man because of their low cost and common use. These raw vegetables were also believed to be indigestible and harmful "if not by doctor's prescription or their evils lessened by cooking". "The medieval cuisine consisted chiefly of soup and soup meats and the exceptions to this rule were few."

Man's struggle for his bite to eat must have made an indelible impression on his mind. He was often tired, hungry and thin, and if by chance he secured an adequate amount of food he immediately felt well and strong again. This fact together with

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the fact that man's diet has varied with the locality, the climate and the soil, and the proximity to large bodies of water without any markedly different effect upon his mental or physical development must have indicated to the physicians, at least, that the quantity of food was of much more importance than its character.

Early medicine developed about the diet and the care of the gastrointestinal tract and the patient "went to the same professor for physic and food". Therefore, it was only natural that Hippocrates, Galen, Morten, Reed, Bayle, Laennec and numerous other physicians and writers should all stress the importance of diet in the treatment of any disease such as tuberculosis which is characterized by loss of weight and strength. So much attention was paid to the palatability of the food in the hope that the patient's appetite would be stimulated and thus compensate for the loss of weight, that "a culinary recipe was often considered a remedial prescription".

While the idea of the importance of diet in the treatment of tuberculosis was based on an inaccurate knowledge as to its cause, nevertheless this apparently logical treatment has become so firmly entrenched in the therapeutics of the professional and lay worlds that many still cling to it. In 1835 Clark called attention to the danger of over-feeding the patient, "by which the stomach and bowels are disordered and a new train of symptoms produced which complicates the case and adds to the patient's distress". He also claims that "abdominal congestion leads to a similar condition of the lungs and under such conditions the

patient's life is in imminent danger". This is an actual paraphrase of a statement made centuries before by Hippocrates. Kramer, Grayzel and Shear say that in the olden literature as reviewed by Wells, DeWitt and Long, cod liver oil is mentioned frequently as having great value in the treatment of tuberculosis. Williams, in the early part of the 19th century, claimed that in his opinion "cod liver oil had done more for tuberculosis than all other measures put together". We now realize that its value is probably due to its vitamin content. Unfortunately some people have such a low fat tolerance that they are unable to use cod liver oil and the vitamin content varies with the quality of the cod liver oil. Even as late as the early part of this century, the treatment of tuberculosis consisted of fresh air and an attempt to over-feed the patient. Instances are on record of patients attempting to consume—and they occasionally actually succeeded—a diet of 5,000-7,000 calories per day with frequently disastrous effects upon the gastrointestinal tract. In 1908, Fisher reported that ninety-five sanatoria located in various parts of the world served a diet of 2,140 to 5,500 calories per day with a protein content of from 60 to 190 grams. Recently, due to a better understanding of the pathology of tuberculosis, the over-feeding of patients has ceased in our larger sanatoria but there are still many physicians who believe that tuberculosis is cured by a high protein diet.

If we couple the economic background of an inadequate food supply with the medical background which is based on the picture of tuberculosis as

it is characterized by the word "consumption", we at once see the reason for the importance of diet in the treatment of tuberculosis.

In 1919, McCann applied the modern methods of study of nutritional requirements of man to the dietetic requirements of the tuberculous. As a result of these studies he estimated that the daily energy requirements of the consumptive at absolute bed rest ranged from 1760 to 2640 calories per day. The estimation was founded upon the basal heat production plus additions to the diet in accordance with the amount of fever present. He also called attention to the apparent antagonistic metabolic factors in a disease causing abnormal wasting which should be corrected by a high caloric diet but whose cure lies in pulmonary rest. While such a diet might counteract the wasting, yet the resulting accelerated metabolic rate would increase the pulmonary activity. This is contrary to the aim of the present day treatment. Mayer and Kugelmass estimated that the diet which they consider as ideal for the tuberculous individual would accelerate metabolism thirty-seven per cent and hence interfere with the desired pulmonary rest. McCann and Barr in 1920 concluded that as "the food requirements of tuberculous patients are not large either as regards total energy value or nitrogen content, forced feeding is unnecessary and is probably harmful in the active stages of pulmonary disease. Since protein increases the respiratory exchange in the tuberculous as well as the normals it may be well to limit the protein intake during periods of activity in order to put the lungs at

rest." Therefore, it seems that the ideal diet for the consumptive is one which will enable the individual to maintain normal nutrition and his sense of well-being with a minimum amount of pulmonary activity. McCann believes that this can best be obtained by a diet consisting of sixty to ninety grams of protein with fat up to the limit of digestive capacity and a sufficient amount of carbohydrates to raise the caloric value of the diet to 2500 to 3000 calories per day.

While tuberculosis is distinctly an infectious disease, often accompanied by gastrointestinal and nutritional disturbances, rather than a nutritional one, man is still searching for a diet which will improve the patient's chance for recovery. Recently Sauerbruch, Gerson and Herrmannsdorfer announced such a diet. This represents an attempt on the part of Herrmannsdorfer to adapt a diet, previously used with excellent results by Dr. Gerson in the healing of wounds, to the treatment of lupus and later of pulmonary and bone and joint tuberculosis. He aimed to correct the excessive tissue hydration which occurs in tuberculosis by so planning the diet that the sodium chloride content of the urine is reduced to 0.2 to 0.3 grams per day. This is to be done through the substitution of mineralogen, a mixture of inorganic compounds containing 70 per cent of calcium phosphate and lactate for table salt. While mineralogen contains a preponderance of alkali-forming salts, the German clinicians claim that its chief value lies in its acid-forming properties. Its chemical composition, together with the fact that a number of its con-

stituents are absorbed so slightly in the alimentary canal that they can have very little if any effect upon the acid-base equilibrium, makes this contention very doubtful.

The diet permits fifty calories per kilogram weight per day with an average maximum of 3500 calories in the ratio of protein 1.5, fat 1.7 and carbohydrate 3.7. This gives a protein allowance of 92 grams per day which the Europeans consider low but which we do not, as the diet in the average American sanatorium consists of 70 to 100 grams of protein. The fat content of this diet is relatively high and the carbohydrate content relatively low because carbohydrates reduce resistance to infection in general. The chief sources of protein are milk and eggs and milled products, as only 500 grams of fresh meat are permitted weekly.

One of the outstanding features of this diet is a relatively large amount of vitamins from A to G inclusive. Fruits and vegetables, either fresh or cooked, which are abundant in vitamins, are used freely as is phosphorated cod liver oil, a teaspoonful of which is given with each meal. The list of restricted and permitted foods is long and has been given elsewhere, so it will be omitted from this discussion. Every attempt, however, is made to improve the palatability of the food and to compensate for the lack of its salt. In Munich the results of this diet have apparently been extremely beneficial in lupus but not so beneficial in bone and joint tuberculosis and its value in the treatment of pulmonary tuberculosis has not been so easily determined.

Mayer and Kugelmass' report on twenty patients at Saranac Lake who failed to gain on the accepted therapy over a period of two or three years previous to the use of this diet is very interesting. On this diet the symptoms improved; there was partial x-ray clearing in about a third of the cases but the sputum remained positive in all cases. Two very stubborn cases of intestinal tuberculosis cleared up clinically and x-ray filling defects of the colon disappeared. The results obtained were in general accord with those obtained in similar studies made on rats maintained on an acid forming and base forming diet respectively. Clarence Emerson, of the Lincoln General Hospital, reports favorably on a series of 40 patients treated with this diet over a period of twelve months. While he is apparently not unduly enthusiastic about it, still he believes that this diet favors an improvement in tuberculosis. Martin, on the other hand, believes that one should strive for a slight alkalosis of the blood and tissues rather than for an acidosis, while Von Baeyer reports that his tuberculous patients thrive on a dry diet.

Myers stresses vitamin A particularly, while McConkey and Smith believe that all vitamins are of extreme importance in tuberculosis and other chronic infections. McConkey reports that the healing of intestinal ulcers is markedly improved through the administration of cod liver oil and tomato juice, rich sources of vitamins A, B, C and D. He also claims that the oral administration of 2.5 grams of irradiated cholesterol, 1 gram of concentrated cod liver oil and 10 grams

of irradiated yeast daily is just as effective in the treatment of intestinal tuberculosis as is artificial heliotherapy. He adds, however, that irradiated cholesterol is apparently less effective than the others as it was fed to nine children with bone and joint tuberculosis for four months without any appreciable effect upon the healing process or increase in blood calcium or phosphorus. His report calls attention to the fact that apparently there is close relationship between the beneficial effects of heliotherapy and the increased formation of vitamin D as a result of the solar radiation.

The research work on the effect of diet in experimental tuberculosis seems to center about the use of calcium and the vitamins. Because calcium is so frequently found in healed lesions of tuberculosis, numerous attempts have been made to influence the rapidity of the healing process by increasing the blood calcium. That naturally raises the question as to whether there is a diminution in blood calcium in tuberculosis. According to Greisheimer and Van Winkle, tuberculosis is not characterized by a demineralization although the "C" group of cases showed lower calcium value than any of the other groups. Gordon and Cantarow claim that an increase in the normal calcium content of the blood has apparently no influence on the tuberculous process. McRae and Ingvaldson claim that "as vitamin D causes calcification in rickets, we may conclude that it should do likewise in tuberculosis". Grant, Bowen and Stegeman conclude that when calcium and vitamin D are decreased sufficiently there is a definite lowering of

the resistance to tuberculosis in rats and conversely that rats maintained on adequate diets could withstand many times the dose of tubercle bacilli which produced tuberculosis in rats maintained on a deficiency diet. Because of this they believed that the vitamin D content of the diet should be increased in gloomy weather to compensate for the lack of sunshine. An analysis of Grant's report in 1930 warrants one in concluding that she believes that when a diet is deficient the addition of vitamin D does not retard the tuberculous process but if the diet is already adequate a further addition of vitamin D seems to increase the resistance to tuberculosis, though a prolonged excess of vitamin D seems to lower it. She called attention to the fact that resistance to tuberculosis can be reduced by a prolonged disturbance in the optimal balance which should exist between calcium and vitamins C and D of the diet *without destroying the growth impulse*. McConkey and Smith claim that a diet partially deficient in vitamins A, C and D renders guinea pigs susceptible to intestinal tuberculosis. They believe that "a chronic partial deficiency of vitamin C is the most important factor in the production of clinical disease."

As the importance of vitamins in the diet is generally accepted, the question of the value of commercial preparations of vitamins is raised. In this connection McCollum writes "The fact that we can readily prepare diets from ordinary foods which will contain several times the minimum amount of vitamins upon which apparently normal nutrition can be maintained over a considerable period of

time, tends to render academic the discussion about the advisability of taking concentrated commercial preparations of vitamins."

Hawes' report of the answers of thirty-six physicians to the following eight questions is very interesting as it indicates modern practice.

1. Do you believe in lunches between meals? If so, under what conditions? Lunches between meals are rarely advisable. The average patient enjoys his food more and takes larger amounts of nourishment when he confines himself to three meals a day than in any other way.

2. Do you advise egg-nogs? Egg-nogs in any form at any time are as Dr. Carroll Edson says, "An invention of the devil."

3. Do you believe in raw eggs? If so, how do you advise the patient to take them? Raw eggs are easily borne and if the patient is under weight, do not do any harm and may do good. They are not so digestible as cooked eggs and on the whole are rarely indicated.

4. As a general proposition, how much extra milk is advisable? About one quart of milk a day, four or five glasses with meals, is the maximum amount that should be given. A glass of milk with each meal is usually sufficient.

5. Do you lay down any definite laws about what special foods should be emphasized? There are no special foods that need be emphasized. Fruits and vegetables will help correct constipation. They contain vitamins but little if any nourishment. Potatoes, macaroni and rice contain much food value.

6. Do you give any special directions about the care of the bowels? The bowels should act at least once daily. A mild laxative once a week is often a valuable help if a diet with plenty of roughage is not enough.

7. Do you advise using large quantities of water? Five or six glasses of water with and between meals is advisable in every case.

8. Do you emphasize rest before and after each meal? A rest before and especially after each meal is essential. The dictum approach and leave each meal in a rested condition is an especially good one to adhere to.

Modern man has so developed his food supply that the poor man of today has a more varied and stable diet than did the wealthy man of a few centuries ago. For instance, due to the improvements in the canning industry we now have vegetables the year around. Therefore we no longer feel as run down in the spring as did our ancestors who took sulphur and molasses as a spring tonic.

But even with his wonderful opportunities for a stable and well-balanced diet, modern man, particularly in Europe and America, is, in the opinion of McCollum, deriving too large a proportion of his food from cereals (35 to 45 per cent) supplemented by muscle meats, potatoes and sugar. He states that this combination of food does not support satisfactory development, longevity and fertility in any of the animals with which experimental studies have been conducted. Cereals which form the bulk of the diet are comparatively cheap but when used singly are deficient in proteins. When used in various combinations the pro-

tein deficiency of one individual cereal is supplemented by the protein content of another. Muscle meats are similar to cereals in that they are deficient in calcium and sodium chloride but they have become very palatable and modern man is using them freely to the exclusion of the rest of the carcass, thereby losing the protective foods which it contains. If man used more of the carcass as does the carnivorous animal, his diet would be better balanced and would not need to be supplemented by the protective foods. Carbohydrates, with the exception of honey which contains a small amount of vitamin B, are lacking in vitamins and their excessive use lowers the resistance of the body to infection in general.

Because of the deficiency of the above diet, it is necessary to supplement it by certain protective foods in order to improve nutrition and skeletal development and to increase the resistance of the body to infection in general. Milk, eggs, leafy vegetables and fruits belong to this group of foods. Milk is a very satisfactory article of food but it is inadequate when used as a sole source of nourishment over a long period of time. When used in combination with other foods, it supplies their deficiency. Eggs are also very valuable for increasing the palatability of other foods, and are rich in vitamins A and D but poor in vitamin B. They are also deficient in calcium and favor putrefactive processes in the gastrointestinal tract but this tendency is counteracted when combined with carbohydrates and milk. Sea foods are very satisfactory sup-

plementary foods because the entire edible portion of the animal is used.

McCollum calls attention to the fact that there are two general types of deficiency diets, one which is marked and is followed by an acute reaction as beri beri or scurvy and a slight borderline deficiency which must be continued over a long period of time before its effect is felt. It is this latter type of deficiency diet which, because of its insidious nature, is so pernicious and harmful for man. There is much evidence to show that a good state of nutrition increases greatly the resistance of the body against certain types of infection while, on the other hand, an improper diet will cause inferior physical development, lack of recuperative powers and endurance and may result in accumulative fatigue with a lack of resistance to those infectious diseases where specific immunity is not usually developed.

That the skeletal development of man can be markedly influenced by diet is evidenced by the fact that the Japanese children born in this country and fed on an American diet will in the second and third generation be considerably larger than children of the same age who lived on a Japanese diet. Grant's conclusions also call attention to the fact that there is of necessity no specific relationship between the skeletal development or size and weight and resistance to tuberculosis. Russell reports as the result of his clinical observation on a number of dispensary cases, that while nutrition may have a marked effect upon the symptoms of tuberculosis, it failed specifically to effect the course of the disease. That recalls a statement of Stewart

"that we put patients to bed because of symptoms and a lesion. We are prone to forget about the lesion and let them up when the symptoms have disappeared." Loss of weight is one of the symptoms of tuberculosis and we are all too apt today to forget about the lesion when the symptoms have disappeared and man's nutrition is back to normal or a little above and to conclude, as did the ancients that the individual is well.

CONCLUSIONS

There is much evidence to prove that there are certain minimum requirements as far as proteins, fats, carbohydrates, vitamins and minerals are concerned in order that normal health may be maintained. Metabolic studies in tuberculosis prove that increasing the diet beyond a certain point is detrimental to the cure of pulmonary tuberculosis because of the increased pulmonary activities necessitated by the increase in metabolism. As we believe that a diet which is well balanced and adequate for a man in health is sufficient as the basic diet for the person with tuberculosis, Glen Lake Sanatorium has prepared such a diet which, unless there is definite gastrointestinal pathology, or nutritional disturbances present, is essentially the same as would be provided for the non-tuberculous individual who is living under the same relative conditions of exercise. When, however, such conditions are present, they should, of course, receive just as prompt and careful treatment as they would, should they occur in a person without tuberculosis. The diet as planned provides

for about 3000 calories per day and includes half a pint of milk with each meal and at bed time, and contains 70 to 100 grams of protein and about 300 grams of carbohydrates. The balance is composed of fat. Those who are below weight receive an extra half pint of milk in the morning and afternoon. Of course, this is merely the basic diet and is modified as occasion demands. Out of a population of 640 adults we have at times served as high as a 125 special diets.

In planning this diet we have followed the general suggestions of McCollum as to the most satisfactory type of diet which represents "the best elements from those several systems of diets which have been thoroughly tested in human experience and have been found successful". In brief, these are, that if the protective foods such as dairy products, including one quart of milk daily and leafy vegetables, are used freely and also a certain amount of raw vegetables and fruits for their antiscorbutic properties (we use a fairly large amount of canned vegetables also which if one can judge from Byrd's two years' experience at the South Pole are also antiscorbutic) "the remainder of the food supply may safely be derived from any of our ordinary milled cereal products, tubers, root vegetables, sugar, and meats. Infants and children can be safeguarded in their skeletal development by providing at regular intervals a suitable amount of cod liver oil, and by affording an opportunity for outside exercise in sunlight."

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Editorials

BLOOD CHANGES IN BENZOL POISONING.

In the nine years since Schultz described the condition now known as agranulocytic angina, it has become a disease of frequent occurrence. It is now evident that it is not an entity as was first believed, but rather a group of conditions; for in some cases there is granulocytopenia without angina, in others a severe aplastic anemia, and in still others a hemorrhagic diathesis dominates the clinical picture. Likewise there is a wide range of conditions with which granular leukopenia may be found associated: radium and X-ray irradiation, administration of arsenic compounds and especially arsenophenamine, benzol and its homologues and substitution products, and with pernicious anemia, aleukemic lymphoblastoma and lymphatic and myelogenous leukemia. With these there may or may not be sore mouth and angina. A necrotizing process against which the defensive powers of the body are powerless, or nearly so, may seem to have its origin in an operative wound, or to arise *de novo* on parts well away from the mouth. Does this group of morbid conditions constitute a new disease-concept or have we always had it with us? Is the apparent wave of leucopenic, aplastic anemic, and myelophthisic conditions, variously styled, the result of directed attention and therefore of better diagnosis? It so happens that certain of the known agencies capable of producing similar

effects upon the bone marrow and blood are those whose industrial and therapeutic use is rapidly increasing. What part of the increase may be thus explained no one can as yet determine.

The effect of benzol upon the blood and blood forming organs has been studied from the standpoint especially of the important industrial hazard which exists. Benzol (*benzene*, not *benzine*) is used for its solvent action, its fuel value, and as a starting point in the manufacture of various synthetic drugs, dyes and other products. It is employed in a variety of industries, including many branches of the manufacture of rubber, artificial leather and leather enamels, waterproof fabrics including rubber raincoats, window shades, lacquers, shellacs, paint removers, bronzing liquids and batteries, in dry cleaning, and in many other ways. For the past six years the annual production of benzol in this country has not fallen below 100,000,000 gallons.

In the present year two very important studies of benzol poisoning have appeared: a comprehensive review by Alice Hamilton* and an analysis of the literature with much original material added, by Carey P. McCord.**

*ALICE HAMILTON, M.D., Benzene (benzol) poisoning, Arch. of Path., 1931, xi, 434-454; 601-637.

**CAREY P. MCCORD, M.D., Benzol (benzene) poisoning; a new investigation of the toxicity of benzene and benzene impurities, 1931, from The Industrial Health Conservancy Laboratories, Cincinnati, Ohio.

Their conclusions in regard to the blood are especially important. In the early stage of benzol action a leucopenia is not found, but on the contrary, the white cells are usually moderately increased. Continued exposure leads to a significant leucopenia, oftentimes as low as 500 cells per cubic millimeter if exposure is continued. Very rarely a leucocytosis persists. The establishment of an arbitrary level of depression of the white count as indicative of benzol poisoning has certain inherent dangers. The normal variation of an individual may swing over a range in which the maximum is 100 per cent greater than the minimum. Thus a fixed standard, such as that a decrease of 25 per cent from the normal white blood cell count constitutes a fair index of the presence of benzol poisoning, providing other conditions can be ruled out, must be applied with caution. Nevertheless, in the presence of this industrial hazard a sustained leucopenia of 25 per cent or more as based upon a knowledge of normal counts of the individual, is of diagnostic value; and any white blood cell count in the neighborhood of 5,000 or less in a benzol worker is fair evidence of poisoning if this degree of leucopenia persists in several counts distributed over one or more days. The red cells suffer a less severe reduction than the white cells. In the late stage of cases destined to be fatal red blood cell counts as low as 1,000,000 or even 500,000 have been found. Under the influence of benzol, basophilic red cells are present in numbers far higher than normal and occasional nucleated red cells are seen, but poikilocytosis, anisocytosis and hemolysis are by no means

constant, and in respect to these the literature is conflicting. The hemoglobin falls in proportion to the diminution in red blood cells, for the anemia is dependent upon injury to the bone marrow and not upon hemolysis. McCord was unable to find significant points of differentiation between the blood picture of benzol poisoning and that of the agranulocytosis of Schultz's angina. In all but the early stage of benzol poisoning the platelets are decreased and bleeding time is frequently prolonged. With platelet counts below 30,000, spontaneous hemorrhages are said to appear. Finally, and of great significance in duplicating the picture of agranulocytic angina, it has been shown by numerous workers that benzol may lower the infection-resisting powers of the body by diminishing antibodies. In fatal cases of chronic poisoning with benzol, infection nearly always plays a part and not infrequently necrotizing infectious lesions of the mouth are present. Thus in seeking extrinsic factors in the etiology of the leukopenic diseases benzol and its allies must be kept constantly in mind.

SAFETY FIRST

Seldom, indeed, has the physician been found deaf to a legitimate call for his services, a shirker when confronted with duty, or a coward. Neither has his apparent disregard for personal comfort and security been based upon ignorance of possible consequences to himself. At the present time it must be exceedingly rare for an emergency to arise in which a physician finds it necessary to aspirate a diphtheritic membrane from the

larynx of a dying child by mouth to mouth contact. It was not the discovery of the Klebs-Loeffler bacillus, however, which caused this act of heroism to become all but unknown at the present time. That the physician is responsive to duty without regard to himself is generally known, and the resulting situation has become part of the stock in trade of the outlaw. According to press reports, a Fellow* of the American College of Physicians received an emergency call over the telephone requesting him to go to a certain address, with the added appeal, "Please come quick, doctor; the baby is dying of pneumonia." Experiencing some difficulty in finding the number given, he was lured into a dark, and as afterwards appeared, vacant house by a man in the doorway who said, "Please hurry, doctor." Within the house he was struck repeatedly with a black jack, robbed of money and wrist watch, and left dazed and apparently unconscious. After an interval he was able to recover his keys from the floor, reach his car, drive home, and summon aid. Such incidents have become increasingly more frequent. Robbery always has been the motive with sometimes assault added, as in the example recounted, or kidnapping. In the face of another year of economic stress, it cannot be hoped that the danger will be lessened. In some cities this situation has been met by arrangements with the police departments such that a physician answering night calls can, if he desires, have escort, or be met at the stated address by a police officer. This is easily man-

aged where radio-controlled scout cars are used for night patrol. The physician telephones his destination and time of arrival and his escort meets him at the address given or at a nearby street intersection. Through existing organizations physicians can properly request such aid in the performance of their recognized duty. Where similar plans are already in operation, physicians should not hesitate to avail themselves of the protection offered.

THE STANDARDIZATION OF AMERICAN SPECIALISTS

Several articles have appeared in the medical press of America during recent years concerning what might be termed the standardization of specialists. Under present conditions anybody who chooses to, provided he is qualified and registered, can set up office as a specialist in any of the many branches of medicine. He may or may not have any particular knowledge of the subject he professes to specialize in. I think, however, the great majority of men make it their business to take special instruction over a period of six to twelve months in the subject or subjects they wish to specialize in. The public as a whole expects great things of the specialist, and certainly takes it for granted that he possesses infinitely superior knowledge of his subject than his unfortunate much-maligned brother, the general practitioner; the public occasionally is quite wrong in this supposition. It would certainly appear that a more or less fixed standard is necessary, and as far as medicine is concerned I am of opinion that the American College of Physicians can be of tremendous

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assistance in dealing with this problem. It should be a sort of "*sine qua non*" that no physician could be accepted as having joined the ranks of specialism proper unless he possessed at minimum the Associateship of the American College of Physicians. In some way or other the general public should be thoroughly instructed and made to understand this. It would be well if the Board of Regents and the Committee on Credentials at an early date very carefully considered the important and pressing question of holding an examination proper either written or clinical or both for admission to Associateship in the College; this might be held after the ordinary pre-

liminaries of investigation of the candidate's worth and suitability for nomination have been gone into in the usual way by the Executive Secretary and Committee on Credentials. This, to my mind, is the only practical way of facing the problem, and the examination of the American College of Physicians will have to be looked up to and known throughout the country as the hall-mark of specialization of the American continent, so far as medicine is concerned.

(Contributed Editorial by G. A. PEMBERTON WRIGHT, F.A.C.P.; M.C. P. and S. (Ont.); L.A.H. (Dub); Ph.C. (Irel.), Kingston, Jamaica.)

Abstracts

Der Abbau des Blutfarbstoffes im Verdauungstrakt des gesunden Menschen. (The Breaking Down of Blood Pigment in the Digestive Tract of Healthy Men.) By FELIX HAUROWITZ. (Arch. f. Verdauungs-Krankh., 1931, 1, 33-46.)

After the ingestion of 50 c.c. of the subject's own blood, the feces were subjected to chemical analysis in order to determine the amounts of the various derivatives of blood pigment present. Control analyses were made for several days before ingesting the blood and the subject was maintained on a blood- and chlorophyll-free diet. By far the greater part of the blood pigment was recovered on the second and third days following ingestion as protohemin. Three groups of analyses showed an output of 85 to 90 per cent as protohemin, 5 to 8 per cent as deuterohemin, 2 to 3 per cent in the protoporphyrin fraction and $\frac{1}{2}$ to 1 per cent in the deuteroporphyrin fraction. The excretion of coproporphyrin was not significantly influenced by the ingestion of blood. Deuterohemin, and proto- and deuteroporphyrin are not derived from blood pigment through the agency of enzymes but through putrefaction. Native blood pigment (oxyhemoglobin and reduced hemoglobin) was not found in the stools. This is in agreement with the known rapid alteration of native blood pigment produced by gastric acidity. On the other hand alkaline trypsin solution alters blood pigment so slowly that native blood pigment may be demonstrated even after 24 hours. Thus the demonstration of occult native blood pigment (by its characteristic spectrum) in the feces comes to be of diagnostic significance in differentiating between bleeding into the acid stomach contents, or into an achyl stomach or the alkaline upper small intestine, providing a source of blood from a lower level can be excluded. Methods for the analysis of feces for the qualitative and

quantitative recognition of the various blood pigment fractions are given in detail.

The Elimination of Phenolsulphonphthalein by the Kidney: The Influence of Pathologic Changes in the Liver. By J. P. HANNER, M.D., and G. H. WHIPPLE, M.D., Rochester, N. Y. (Arch. Int. Med., 1931, xlviii, 598-610.)

For many years it has been known that an unusually high degree of renal elimination of phenolsulphonphthalein occurs in certain cases of toxemia of pregnancy. It was suspected that these cases were complicated by some abnormality of the liver. This question has been investigated by carefully controlled experiments in which liver injury has been produced in dogs by various means, and also by the determination of the mode of excretion in animals with complete obstruction of the common bile duct. It was found that the normal dog excretes from about 10 to 15 per cent of the usual dose of phenolsulphonphthalein by the hepatic route. When this pathway is blocked, the surplus appears in the urine, giving figures proportionately higher than would otherwise be found. Of that portion which escapes into the intestines in the normal animal, not more than 5 per cent is absorbed, so that reabsorption of the dye from the bile can be dismissed as a factor of no importance. In dogs with necrosis of the liver due to chloroform poisoning there is a distinct rise in the elimination of phenolsulphonphthalein by the normal kidney. With repair of the hepatic injury, the elimination of phthalein returns to normal. Phosphorus gives a similar but less striking reaction. After hepatic injury due to chloroform, the dog's liver does not remove phenolsulphonphthalein from the blood stream and does not excrete it in the bile. The portion which otherwise would have been removed by this route is therefore available

for excretion by the kidneys. Clinically, therefore, an unusually high renal elimination of phenolsulphonphthalein should suggest pathologic changes in the liver; and in the presence of combined renal and hepatic disease, great caution should be exercised in the estimation of the amount of renal injury.

A Study of the Blood Picture in Congenital Syphilis and the Effect of Antisyphilitic Therapy upon the Hemoglobin and Cellular Elements. By H. HARRIS PERLMAN, M.D., and CARROLL S. WRIGHT, M.D. (Am. Jr. Syph., 1931, xv, 449-495.)

Thirty-four patients with congenital syphilis were selected for this study. Diagnosis of syphilis was based upon history of the disease as existing in either parent, with clinical or roentgenographic manifestations and positive serologic reactions in the child. In age, these patients ranged between 2 and 14 years. Twenty-seven normal children within the same age range were used as a comparative normal control, and as a further control a group of 22 non-syphilitic, but under-nourished, children was established. It was found that the secondary anemia present in congenital syphilis does not differ from the anemias associated with various chronic infections; and that in both degree and kind, it may not differ from anemias which are discoverable in supposedly healthy children. No reliance could be placed upon the degree of anemia as a diagnostic sign, nor did the study of the individual cell types of the blood reveal anything of diagnostic or prognostic importance. Blood studies were carried out before and after various forms of antisyphilitic therapy. Arsenic or bismuth or a combination of these drugs was found to have a variable and inconsistent effect upon the secondary anemia and upon the differential count. In certain groups there was a greater loss than gain in hemoglobin, but in no single series was there any striking change referable to the treatment used.

A Study of Nephritis at the Canton Hospital. By WILLIAM W. CADBURY, A.M., M.D., F.A.C.P. (Transactions of the Eighth Congress of the Far Eastern As-

sociation of Tropical Medicine, Bangkok, December, 1930. 19 pages.)

There is very little to be found in medical literature concerning nephritis among native Chinese. The general impression that Bright's disease is less prevalent in China than in Europe and America seems to be borne out by such statistics as could be collected, but the difference is not very great. In twenty-three institutions in China it was found that the percentage of nephritis to all hospital admissions varied from 0.25 to 1.00 in ten, from 1.02 to 1.69 in eleven, and in only two did the ratio exceed 2.00 per cent. In five large hospitals in the eastern part of the United States relative incidence of nephritis to all cases admitted varied from 1.33 to 3.18 per cent. The percentage of nephritis cases to medical admissions only was between 2 and 3 in four Chinese Hospitals, between 3 and 4 in five, 4.04 at Canton Hospital, 4.09 at Peiping Union Medical College, and over 6.00 at Hackett Hospital in Canton and the Government Civil Hospital in Hongkong. In the five hospitals of the United States, with which comparison is made, the incidence of nephritis to medical admissions varied from 3.63 to 7.61 per cent. A larger proportion of nephritis cases was found in the hospitals of south and central China than in those of north China.

The Effect of Cortin in Asthenia. By FRANK A. HARTMAN and GEORGE W. THORN. (Proc. Soc. for Exp. Biol. and Med., 1931, xxix, 48-50.)

The effect of cortin in the asthenia of a number of clinical conditions including Addison's disease has been investigated. Since increased susceptibility to fatigue is more significant in such conditions than the actual dynamic power of the muscle, a finger ergometer was used to test the threshold of fatigue. Four normal individuals showed a maximum increase in power to do work before the development of fatigue of from 50 to 500 per cent. The effect of cortin on the fatigue point was studied in six cases of Addison's disease, two in which the cortical insufficiency was almost absolute and four in which it was less marked. The threshold of fatigue was advanced 700 per

cent in one of the severe cases and none in the other. One of the less severe cases showed no increase; two increased 400 per cent and the fourth, 4900 per cent. Other conditions associated with asthenia, in which improvement in susceptibility to fatigue, either symptomatic or ergometric or both, followed administration of cortin, were pregnancy, Graves' disease, muscular dystrophy, osteomyelitis, diphtheria and myasthenia gravis.

Cerebral Adiposity with Mental Deficiency and Retinitis Pigmentosa: The Lawrence-Biedl Syndrome. By EDWARD WEISS, M.D. (Endocrinology, 1931, xv, 435-441.) Lawrence and Moon in 1866, Bardet in 1920, and Biedl in 1922, described a familial condition in which the affected individuals show retinitis pigmentosa, adiposity, genital hypoplasia, night-blindness, polydactylism and mental deficiency. This has since been called the Lawrence-Biedl syndrome and

the Bardet syndrome. The author adds the forty-eighth to the list of the reported examples of this syndrome. His patient was a girl, whose life age was fifteen years and eight months, and her mental age approximately five years. She was obese, weighing 194 pounds and had six toes on each foot. There was partial paralysis of the external rectus muscle of each eye, retinitis pigmentosa, and genital hypoplasia of moderate degree. It was formerly considered that this condition resulted from a disorder of the pituitary gland. More recently the tendency has been to regard a lesion of certain metabolic and genito-trophic centers in the floor of the midbrain as responsible. This is explained embryologically as dependent upon a genetic defect of the forebrain. Treatment with glandular extracts, chiefly thyroid and pituitary, has brought about improvement in some cases. This was true of the case reported.

Reviews

Human Heredity. By ERWIN BAUR, Professor of Heredity at the Agricultural Academy in Berlin; EUGEN FISCHER, Professor of Anatomy and Director of the Anatomical Institute at the University of Freiburg, Breisgau; and FRITZ LENZ, Professor of Racial Hygiene at the University of Munich. Translated by EDEN and CEDAR PAUL. 734 pages, 172 illustrations, and 9 plates. The Macmillan Company, New York City, 1931. Price, \$8.00.

This book is an English translation of the third edition of *Menschliche Erblchkeitslehre*, which was published in Munich in 1927, with supplementary material supplied during the preparation of the English version. The text is divided into five sections. The first section, by Baur, reviews briefly and clearly the general theories of variation and heredity. The second part, contributed by Fischer, treats of racial differences in mankind. From a consideration of the characters responsible for the differ-

ences in the external appearances of individuals the author proceeds to a discussion of racial origins and racial biology, and a description of the races of mankind. In classifying the so-called normal types of man, the author follows the usual German method of division into asthenic, pyknic, and athletic groups. Yet a considerable proportion of "normal" individuals fail to conform to any one of these three classes, so that this classification is far from satisfactory. The final three sections are all by Lenz and deal with morbid hereditary factors, with methodology in human heredity and with the inheritance of intellectual gifts, respectively. Many will find it impossible to subscribe to the definition of disease as "the state of an organism which is on the borderline of its capacity for adaptation," when such a conception causes the author to designate color blindness as an anomaly not coming within the category of disease. Practically all disease conditions

in which the hereditary factor is important in etiology are considered in this section and genealogical diagrams are presented for many of them. The importance of heredity in the etiology of neoplasms is recognized and discussed and here the genealogical tree of the remarkable cancer family described by Warthin is reproduced. Rather more weight is given to the factor of hereditary predisposition in the causation of rickets than is generally accepted. Distinction is made between *blastophthoria* and *idiokinesis* in that the latter term is limited to hereditary alterations in the germ plasm induced by extrinsic agents. The work of translation has been unusually well done. The style is clear and free from the original idiom. This book should be read by all who are concerned with the medical and genetic aspects of the inheritance of disease.

Diagnostic Methods and Interpretations in Internal Medicine. By SAMUEL A. LOEWENBERG, M.D., F.A.C.P.; Associate Professor of Medicine, Jefferson Medical College; Assistant Physician to the Jefferson Hospital; Visiting Physician to the Philadelphia General Hospital, the Northern Liberties Hospital and the Eagleville Sanatorium for Consumptives; formerly Assistant Professor of Physical Diagnosis at the Medico-Chirurgical College and the University of Pennsylvania, Philadelphia. Second Revised Edition. xxiii + 1032 pages. 547 illustrations, some in colors. F. A. Davis Company, Philadelphia, 1931. Price \$10.00 net.

This second edition of Loewenberg's *Diagnostic Methods* contains new material on the cardiac blood supply and innervation, massive pulmonary collapse, coronary thrombosis, hypertension and hypotension, sickle cell anemia, von Jaksch's anemia, agranulocytic angina, acute mononucleosis and the diagnostic importance of certain findings in the cerebro-spinal fluid. In order to incorporate some of this it has been necessary to interpolate a few new pages which are lettered in order to avoid complete re-paging. The well chosen illustrations and diagrams continue to be one of the valuable features of this work. The half-tones are not always satisfactorily reproduced but the

difficulty lies in the always present dilemma in choosing between a stock which will do justice to the cuts and one which will keep the volume within reasonable limits of size and weight. Many of the illustrations of gross pathology are of terminal stages or unusually severe manifestations. Perhaps they tell their story all the more emphatically because of this, but they should not be considered type forms. The reviewer is of the opinion that this book will gain in usefulness if, in the next edition, the space which is now devoted to very brief presentations of certain external and largely surgical conditions is utilized for a more complete exposition of the diagnosis of diseases of the internal organs. To illustrate this point, carcinoma of the breast is given seven lines of text and one and one-half pages of illustrations. Not much can be done with the diagnosis of carcinoma of the breast in seven lines, but in that brief paragraph the curious statement, presumably a typographical error, occurs that '*the lymphatic gland becomes enlarged.*' On the opposite page, polythelia, or polythelism, is designated *polythelin*, a form for which the reviewer fails to find authority. Since the diagnosis of carcinoma of the breast could not be presented adequately, it would have been more useful to have devoted this space to fuller treatment of some condition which presents a constant problem to the internist, as, for instance, bronchogenic carcinoma. In the brief discussion of this far from rare condition, no distinction is made, save in the section on radiography, between sarcoma and carcinoma, primary and secondary, in the lung. The general sections of the book rise to a high level of excellence. The difficult chapter on the examination of the respiratory system is especially well done, the many line drawings adding much to the clarity of the exposition and providing the necessary mechanistic explanation for many physical signs. In many respects this is an excellent textbook.

The Infant Welfare Movement in the Eighteenth Century. By ERNEST CAULFIELD, M.S., M.D., with a foreword by GEORGE FREDERIC STILL, M.A., M.D. (Cantab.), Hon. LL.D. (Edin.), F.R.C.P.

(London). xx + 203 pages. 8 illustrations. Paul B. Hoeber, Inc., New York City, 1931. Price, \$2.00.

"To all who are concerned in the welfare of children and in the steps by which the present almost over-anxious care of childhood has been reached, this book by Dr. Ernest Caulfield will be of absorbing interest." Thus wrote G. F. Still in the Foreword. Since in this day and age practically everyone is interested in the welfare of children, the appeal should be practically universal and the reviewer feels that such will prove to be the case. The period dealt with is one in which there was an awakening of an individual and social consciousness of the value of child life. Of the two decades, 1730-1750, it was stated that 75 per cent of all of the children christened in London were dead before they reached the age of five. Children had been regarded as a necessary evil, and evidence of neglect, cruelty, and infanticide is readily attainable from contemporary sources. Within the eighteenth century, however, there was seen at least the beginning of a different attitude toward the child. Thomas Coram, William Cadogan, Jonas Hanway and George Armstrong are those about whom the story of this movement centers. Although historical, this work never becomes a catalog of men or events, and it is enlivened by numerous direct quotations from original sources. To a large circle, both within and without the profession of medicine, this book is heartily recommended.

Diabetes: Its Treatment by Insulin and Diet. A Handbook for the Patient. By ORLANDO H. PETTY, A.M., M.D., F.A.C.P.; Professor of Diseases of Metabolism, Graduate School of Medicine, University of Pennsylvania; Physician in Charge of Departments of Diseases of Metabolism, Hospitals of the Graduate School of Medicine, University of Pennsylvania, and Philadelphia General Hospital; Consultant in Diseases of Nutrition and Metabolism, Shriners' Hospital for Crippled Children, Philadelphia Unit. Fifth revised and enlarged edition. 231 pages; illustrations and tables. F. A. Davis Company, Philadelphia, 1931.

The fifth edition of this handbook has been extensively revised. The section on vitamins has been rewritten and enlarged, the subject of obesity and diabetic hygiene has been discussed in greater detail, and twenty-one pages of sample diets for those following the orthodox dietary rules of the Jewish faith have been added. As is stated in the preface this is a book for the diabetic and not for the physician; but it is not intended to be a substitute for the physician. The latter will find it an aid in giving the patient such a practical working knowledge of diabetes that his intelligent cooperation will be had. It can be recommended safely for this purpose, but the physician should first become thoroughly familiar with its contents in order that no apparent differences in methods or explanations may appear.

Pediatric Education. Report of the Subcommittee on Medical Education, Section on Medical Service, White House Conference on Child Health and Protection. 109 pages. The Century Company, New York and London, 1931.

The adequacy of the medical school teaching of pediatrics as judged by the opinion of the practicing physician, the proper position of pediatrics in the organization of medical schools, the minimum teaching facilities for pediatrics, and salient points to be presented in both undergraduate and graduate teaching are the subjects considered in this report. The basic information used was obtained largely by the questionnaire method and consequently labors under certain limitations. Nevertheless, teachers of pediatrics and medical school executives will find much that is thought-provoking and helpful in the data presented.

On Phasic Introductory and Release Effects of the Cocaine Group on Vessel Preparations and an Attempt at a General Appraisal of Phase Effects. By EDWARD RENTZ, Pharmacological Institute, Riga. Translated and abstracted by LINN J. BOYD, M.D., F.A.C.P., Professor of Pharmacology, New York Homeopathic Med-

ical College and Flower Hospital. 146 pages. Privately printed, 1931.

Frog blood-vessel preparations were used in obtaining the basic data in a comparative study of the effects of cocaine and of a series of related substitution products as used in varying dilutions. The resulting phasic effects are discussed in detail and their theoretical aspects considered in the light of what is known about similar reversible and cyclic modes of behavior induced by other substances. Those interested in this field of investigation will find here a very large material and a reference list comprising 656 items.

Permeabilitätsstudien an der Darmschleimhaut. [Permeability of the Intestinal Mucosa.] Von DOZENT DR. HANS PAFFRATH, Assistant der Kinderklinik der Medizinischen Akademie in Düsseldorf. 115 pages. S. Karger, Karlstrasse 39; Berlin; 1931. Price, Rm. 8.

This monograph is an experimental and clinical study of the permeability of the mucosa of the small intestine with special regard to the etiology of intestinal intoxication of infancy. Apparatus and methods of investigation are described and the results obtained from several groups of substances under varying conditions are analyzed and presented.

American Gastro-Enterological Association. Transactions, 1930. xiii + 169 pages; numerous illustrations. Paul B. Hoeber, Inc., New York City, 1931. Price \$3.00.

In this volume are gathered 27 scientific papers from the thirty-third annual meeting of the American Gastro-Enterological Association held at Atlantic City, New Jersey, May 5 and 6, 1930. Review of each of these is impossible. The eminence of the authors in their respective fields and the selection of the topics as those most significant in present day gastro-enterology are a sufficient earnest of the worth of this collection of reports of original investigations.

Anestesia geral pelo Protoxydo de Azoto [Surgical anesthesia with nitrous oxide].

By Dr. PEDRO AYRES NETTO. Doctoral thesis from the Faculdade de Medicina de São Paulo. 287 pages, 33 ills. Empresa Graphica de "Revista dos Tribunaes", São Paulo, Brazil, 1931.

This thesis contains a detailed study of nitrous oxide as a surgical anesthetic, with survey of the literature and data derived from animal experimentation and personal observations of its clinical use. A bibliography of 250 items is added.

The Psychology of Insanity. By BERNARD HART, M.D. (Lond.), F.R.C.P. (Lond.); Fellow of University College, London; Physician in Psychological Medicine, University College Hospital and National Hospital, Queen Square, London. Fourth edition. xi + 191 pages. The Macmillan Company, New York City, 1931. Price, \$1.25.

This book was first brought out in 1912 and to the present edition, the fourth, but little new material has been added. The relationship of the simple fundamental principles, as previously stated, to the structure of modern psychopathology has been made more evident by a new introductory chapter 19 pages in length and by occasional explanatory footnotes. This book makes no pretense of being a complete treatise at any point. Rather it is an *Einführung* leading the beginner by a logical approach and with proper emphasis upon historical development to the point from which the many independent schools of thought of the present day diverge. For this reason those who seek a full exposition of the theories of Freud will not find them, for so far as Freudism is concerned this book aims to bring only certain selected aspects of Freud's teachings into relation with the lines of advance followed by other investigators, and thus to demonstrate that the conceptions of psychopathology have been built up in accordance with the rules and principles governing the development of other sciences. To the medical student, physician, or to the general reader who desires background material or an introduction to the more obviously technical and partisan treatise, this small book can be fully recommended.

College News Notes

REDUCTION IN REPRINT PRICE LIST

Attention of contributors to the *ANNALS OF INTERNAL MEDICINE* is called to the new price list of reprints appearing on the outside back cover of this journal, beginning with the November, 1931, issue. In quantities of four hundred or more a saving of from twelve and one-half per cent to thirty per cent has been effected and passed on to authors in reduced rates.

This saving is wholly due to a change in the paper stock used in *ANNALS* and in the reprints. Formerly two grades of paper, "antique" for ordinary purposes and enameled stock for illustrations, were used. The mixing of two grades of paper was not only expensive, but detracted from the appearance of the journal. For the November and subsequent issues, through the co-operation of the printers, "Andover plate" is used, making the stock uniform throughout the journal, and adding materially to its appearance.

Dr. James D. Bruce (Fellow and Governor for Michigan), Ann Arbor, Michigan, has been appointed by the Regents of the University of Michigan to the position of Vice President of the University in Charge of University Relations. In this new capacity Dr. Bruce will supervise all of the University's extramural activities. His title at the time of his appointment to a vice presidency was Director of the Department of Post-Graduate Medicine, Member of the Executive Committee of the Medical School and Medical Adviser to the University Health Service.

Dr. Edward S. Calderwood, Dr. Frederick T. Lord and Dr. Joseph H. Pratt (Fellows), Boston, are members of a special Advisory Committee organized for the "purpose of studying the epidemiology, of promoting

prompt diagnoses, of encouraging and facilitating earlier and more general therapeutic use of concentrated serum, of improving methods for serum productions, of correlating the studies on serum production with the results following its clinical use, and of devising procedures for the future prevention, serum treatment and control of pneumonia."

The Commonwealth Fund of New York has made an annual appropriation of \$36,200 for three years to the Massachusetts Department of Health for this study. Various hospitals in different parts of the State will be selected to conduct a special service for pneumonia. Several laboratories will be chosen as pneumococcus type determination stations, and their technicians trained at the expense of the Fund. The Bacteriologic Laboratory of the State Department of Health will continue to make type determinations.

At the Second Annual Fall Clinical Conference of the Oklahoma Medical Society, held at Oklahoma City, November 2-5, many members of the College contributed, as shown by the following report. Dr. James B. Herrick (Fellow), Chicago, and Dr. Leroy S. Peters (Fellow), Albuquerque, were among the distinguished guest speakers. Dr. Herrick delivered an address on "Embolism as Seen by the Internist." Dr. Peters delivered two lectures, one on "Treatment of Tuberculous Cavities," and one on "The Interpretation and Discussion of X-Ray Negatives of the Chest."

Other Fellows who gave addresses are indicated below. Unless otherwise mentioned, they reside in Oklahoma City.

Dr. Arthur White—"Digestive Disorders Due to Lesions of the Stomach;"

Dr. Lea A. Riely—"Digestive Disorders Due to Lesions of Biliary Tract;"

Dr. C. J. Fishman—"Intestinal Indigestion;"

Dr. H. W. Butler—"Anomalies of Heart;"

Dr. Ray M. Balyeat—"Asthma;"

Dr. Leila Andrews—"Functional Heart Disorders;"

Dr. Wann Langston—"Management of Non-Valvular Myocardial Failure;"

Dr. L. J. Moorman—"Modern Methods of Treatment of Advanced Pulmonary Tuberculosis;"

Dr. John Heatley—"X-Rays of Lower Spine;"

Dr. E. S. Lain—"Lesions of the Mouth and their Etiology;"

Dr. Tom Lowry—"Purpura."

Dr. John F. Kenney (Fellow), Pawtucket, R. I., addressed the Rhode Island Medical Society at their last meeting, on "Recent Studies in Etiology of Appendicitis."

At the opening meeting of the Memorial Hospital Staff, Pawtucket, Dr. Kenney read a paper on "Gastric Hemorrhage from other Causes than Ulcer."

Dr. Samuel M. Feinberg (Fellow), Chicago, Ill., addressed the Will-Grundy Medical Society at Joliet, November 4, on "Allergy in Every-Day Practice."

At a meeting of the Royal Academy of Belgium held on June 27, Dr. George R. Minot (Fellow), Boston, Mass., was elected "Correspondent étranger de l'Académie royale de Médecine de Belgique."

Dr. Soma Weiss (Fellow), Boston, Mass., addressed the New York Academy of Medicine at its Fourth Annual Graduate Fortnight, Beth Israel Hospital, New York, October 21, on "Paroxysmal Cardiac Dyspnea."

Dr. William B. Castle (Fellow), Boston, Mass., Assistant Professor of Medicine at Harvard University Medical School and Associate Physician to the Thorndike Memorial Laboratory of the Boston City Hospital, is on leave of absence in Porto Rico where he is undertaking extensive studies

concerning anemia, sprue, uncinariasis and other conditions, and studying further the alteration of gastric function in anemia.

Dr. Kelso A. Carroll (Fellow), formerly of Tucson, Ariz., has accepted the position of Medical Officer in Charge of the Soldiers' Tubercular Sanatorium at Sulphur, Oklahoma.

On the evening of October 6, Dr. Robert M. Moore (Fellow), Indianapolis, Ind., addressed the Vanderburgh County Medical Society at Evansville, on "Some Considerations of the Heart in Surgery."

The following Fellows of the College delivered papers before the Academy of Medicine, Parkersburg, W. Va., November 5, as indicated:

Dr. Henry K. Mohler, Philadelphia—"Auricular Fibrillation; An Analysis of 220 Cases;"

Dr. Louis H. Clerf, Philadelphia—"Bronchoscopy in the Diagnosis and Treatment of Pulmonary Disease."

At the annual meeting of the Montana State Medical Society, held at Bozeman this summer, Dr. Harold W. Gregg (Fellow), Butte, Mont., read a paper entitled "Notes on Early Montana Medical History."

Dr. John Huston (Fellow), Milwaukee, Wis., was recently appointed Medical Editor of the Wisconsin Medical Journal.

At the last regular meeting of the Denver Sanatorium Association, Dr. I. D. Bronfin (Fellow), Denver, was elected President for the coming year.

Dr. Frank Parsons Norbury (Fellow), Jacksonville, Ill., Consultant in Neuropsychiatry, Wabash Railway Hospital Service, delivered a paper entitled "The Importance of the Psychoses as Contributing to Disabilities Among Railway Employees" at the 49th annual meeting of the Wabash Railway Surgical Society at St. Louis, Mo., November 2.

Dr. Oscar W. Bethea (Fellow), Professor of Therapeutics in the Graduate School of Medicine of the Tulane University of Louisiana, delivered an address at Oxford, Miss., October 29, on "Recent Developments of Diagnosis in Chest Diseases."

A medical clinic on Pernicious Anemia recently held by Dr. E. Roland Snader, Jr. (Fellow), Clinical Professor of Medicine at the Hahnemann Medical College of Philadelphia, was published in the October number of the Hahnemannian Monthly.

Dr. Frederic J. Farnell (Fellow), Providence, R. I., was elected a member of the Board of Directors of the American Prison Association, October 21, at Baltimore, Md.

Dr. E. J. G. Beardsley (Governor and Fellow), Philadelphia, Clinical Professor of Medicine at the Jefferson Medical College, held a clinic at the Mercy Hospital, Altoona, Pa., October 27, which was attended by 150 physicians from Blair and adjoining counties.

Dr. Samuel A. Levine (Fellow), Boston, Mass., addressed the New Haven Medical Society, October 7, on "The Clinical Significance of a Systolic Murmur."

Dr. J. W. Torbett (Fellow), Marlin, Texas, was elected Vice-President of the Texas State Medical Association at the last meeting, and was made Chairman of the Committee for Cancer Control to carry on the educational work with the laity and medical profession this year.

During the recent Ninth Annual Clinical Conference of the Kansas City Southwest Clinical Society, held in Kansas City, Mo., Dr. Robert A. Cooke (Fellow), New York City, spoke on "The Clinical Manifestation of Allergy," and conducted a clinic on "The Diagnosis and Management of Asthma." Dr. A. Morris Ginsberg (Fellow), Director of Clinics, conducted a class on "The Differential Diagnosis of Incipient Tuberculosis, Early Thyrotoxicosis and Effort Syndrome."

The following Fellows of the College conducted classes:

Dr. P. T. Bohan, Kansas City, Mo.—Heart Therapy;

Dr. Harry Jones, Kansas City, Mo.—Miscellaneous Heart Disease;

Dr. D. D. Stofer, Kansas City, Mo.—Non-Infectious Heart Disease;

Dr. Sam Snider, Kansas City, Mo.—Pulmonary Tuberculosis—Recent Advances;

Dr. J. V. Bell, Kansas City, Mo.—Pneumothorax in Tuberculosis;

Dr. W. W. Duke, Kansas City, Mo.—Allergy in General Medicine;

Dr. A. C. Clasen, Kansas City, Mo.—Nutritional and Deficiency Diseases.

Dr. Lindsay S. Milne (Fellow), Kansas City, Mo., conducted a clinic on "Valvular Heart Disease," and Dr. A. Comingo Griffith (Governor and Fellow), Kansas City, Mo., gave a clinic on "Rare Medical Cases." Also, Dr. W. A. Myers (Fellow), Kansas City, Mo., conducted a clinic on "Bladder Disturbances Associated with Lumbosacral Lesions."

Dr. Louis H. Clerf (Fellow), Philadelphia, read a paper before the Tri-City Pediatric Society, October 17, held at Philadelphia, entitled "Bronchiectasis in Children: Bronchoscopic Observations."

Doctors Salvatore Lojacono (Fellow), Marquette, Mich., Superintendent of the Morgan Heights Sanatorium, and Frank H. Bartlett, Jr. (Fellow), Muskegon, Mich., Medical Director of the Muskegon County Tuberculosis Sanatorium, were elected trustees of the Michigan Tuberculosis Association at the annual meeting of the organization on October 16.

Dr. Lojacono was recently re-elected Secretary-Treasurer of the Michigan Sanatorium Association.

Dr. George L. Lambright (Fellow), Cleveland, Ohio, gave an illustrated address before the Cleveland Academy of Medicine, October 16, on "Diverticulitis."

Dr. Egerton Crispin (Fellow and Governor), Los Angeles, Calif., was elected

President of the Association of Resident and Ex-Resident Physicians of the Mayo Clinic and Mayo Foundation at the annual meeting held in Rochester, Minnesota, October 8-10.

Dr. Karl Rothschild (Associate), New Brunswick, N. J., attended the International Neurological Congress at Berne, Switzerland, during the past summer. He read a paper entitled "Concussion of the Pons."

Dr. Rothschild was elected a member of the American Psychiatric Association at its recent meeting held in Toronto.

The following Fellows of the College are authors of articles appearing in the September, 1931, issue of the Journal of Laboratory and Clinical Medicine:

Dr. John R. Williams (Fellow), Rochester, N. Y.—"Case Report of Extensive Atrophy of Subcutaneous Fat Following the Repeated Injections of Insulin" (abstracted in the November ANNALS);

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.—"A Method for Urinary Urea."

The Interstate Postgraduate Medical Association of North America held its annual meeting at Milwaukee, Wis., October 19-23, under the presidency of Dr. Henry A. Christian (Fellow), Boston, Mass.

The following Fellows of the College presented clinics as indicated:

Dr. Elsworth S. Smith, St. Louis, Mo.

—Diagnostic Clinic (Medical);

Dr. Harlow Brooks, New York, N. Y.

—Diagnostic Clinic (Medical);

Dr. Henry A. Christian, Boston, Mass.

—Diagnostic Clinic (Medical);

Dr. W. McKim Marriott, St. Louis, Mo.

—Diagnostic Clinic (Pediatric);

Dr. James H. Means, Boston, Mass.

—Diagnostic Clinic (Medical);

Dr. John H. Musser, New Orleans, La.

—Diagnostic Clinic (Medical);

Dr. Cyrus C. Sturgis, Ann Arbor, Mich.

—Diagnostic Clinic (Medical);

Dr. Elliott P. Joslin, Boston, Mass.

—Diagnostic Clinic (Medical);

Dr. Leonard G. Rowntree, Rochester, Minn.—Diagnostic Clinic (Medical).

The following Fellows of the College offered papers as indicated:

Dr. S. F. Haines, Rochester, Minn.—
"The Use of Iodine in Recurrent Exophthalmic Goiter;"

Dr. Elsworth S. Smith, St. Louis, Mo.—
"Cardiac Irregularities Associated with Diseases of the Thyroid Gland;"

Dr. S. Marx White, Minneapolis, Minn.—
"Mechanism and Transmission of Heart Murmurs with a Special Consideration of 'The Unimportant Murmur';"

Dr. William S. Middleton, Madison, Wis.—
"Syphilitic Aortitis;"

Dr. William S. McCann, Rochester, N. Y.—
"Syndrome of Ayerza;"

Dr. Charles A. Elliott, Chicago, Ill.—
"Circulatory Failure in Acute Infectious Diseases;"

Dr. Louis Hamman, Baltimore, Md.—
"Prognosis of Hypertension;"

Dr. Harlow Brooks, New York, N. Y.—
"Coronary Thrombosis;"

Dr. Henry A. Christian, Boston, Mass.—
"Aortic Lesions in Relation to Cardiac Physical Signs and Cardiac Function;"

Dr. Warren T. Vaughan, Richmond, Va.—
"Allergic Diseases;"

Dr. William Gerry Morgan, Washington, D. C.—
"Does Peptic Ulcer Cause Permanent Disability?;"

Dr. W. McKim Marriott, St. Louis, Mo.—
"Infantile Paralysis;"

Dr. James S. McLester, Birmingham, Ala.—
"Recent Advances in the Treatment of Nephritis;"

Dr. Leonard G. Rowntree, Rochester, Minn.—
"Water in Relation to Health and Disease;"

Dr. William A. White, Washington, D. C.—
"Suggestions from Medical Psychology in the Field of General Medicine;"

Dr. B. R. Kirklin, Rochester, Minn.—
"Roentgenological Diagnosis of Early Tuberculosis;"

Dr. Willis F. Manges, Philadelphia, Pa.—
"Bronchial Obstruction, Partial

or Complete as shown by the Roentgen Ray Examination;"

Dr. Paul A. O'Leary, Rochester, Minn.—"Therapeutic Problems of Syphilis;"

Dr. James H. Means, Boston, Mass.—"Significance of Hyper- and Hypometabolism;"

Dr. Hugh S. Cumming, Washington, D. C.—Address;

Dr. James E. Paullin, Jr., Atlanta, Ga.—"Different Forms of Jaundice and their Significance;"

Dr. John H. Musser, New Orleans, La.—"The Medical Treatment of Gall Stones and Cholecystitis;"

Dr. Cyrus C. Sturgis, Ann Arbor, Mich.—"Present Aspects of Treatment of Pernicious Anemia;"

Dr. Elliott P. Joslin, Boston, Mass.—"Complications and Sequelae of Diabetes."

Dr. Austin B. Jones (Fellow), Kansas City, Mo., was recently elected President of the Internist Club, an organization of internists in Greater Kansas City.

Dr. Albert F. Tyler (Fellow), Omaha, Nebr., is the author of an article entitled, "The Treatment of Epitheliomas by Physical Methods," which appeared in the November, 1931, issue of the Nebraska State Medical Journal.

The following Fellows of the College are members of a Committee on Heart Disease, which was recently formed by the Arkansas Medical Society:

Dr. Arthur G. Sullivan, Hot Springs;

Dr. Arless A. Blair, Fort Smith.

The purpose of the Committee is "to acquaint the physicians of the State with recent advances in the diagnosis and treatment of heart disease by publishing articles in the state journal, presenting papers, and sponsoring scientific exhibits at the annual meetings."

At the recent annual meeting of the Kentucky State Medical Association, Dr. Philip F. Barbour (Fellow), Louisville, was elected President, and Dr. C. N. Kavanaugh

(Fellow), Lexington, was elected Orator in Medicine.

Dr. Edwin C. Ernst (Fellow), St. Louis, Mo., acted as chairman of the Local Committee on Arrangements of the Radiological Society of North America, which held its seventeenth annual meeting in St. Louis, November 30 to December 4.

Dr. Ray M. Balyeat (Fellow), Oklahoma City, gave an illustrated address on "Etymology of Allergic Diseases" before the Tri-County Medical Society, October 1.

Dr. William Bernard Yegge (Fellow), Denver, addressed the Boulder County Medical Society, October 8, on "Diagnosis and Treatment of Gastric Ulcer."

During the months of October, November and December, under the auspices of the American Association of Social Workers and the American Association of Hospital Workers, a series of medical lectures for social workers was given at the Medical and Chirurgical Faculty Building, Baltimore, Md. The following Fellows of the College spoke on the dates indicated:

Dr. Henry M. Thomas, Jr., October 19 and 23—"Bright's Disease, Diabetes, Pneumonia" and "Glands of Internal Secretion;" Dr. Thomas also spoke on December 21, on "Diseases of Old Age—Convalescence";

Dr. Lewellys F. Barker, November 2—"Nervous Diseases—Locomotor Ataxia, Paralysis Agitans, Psychoneurotic States";

Dr. Victor F. Cullen, November 10—"Tuberculosis;"

Dr. Louis P. Hamburger, December 15—"Minor Ailments—Aspects of Heart Disease."

The Hennepin County (Minn.) Medical Society was addressed on October 5 by Dr. Moses Barron (Fellow), Minneapolis, on "Purposes and Function of a Medical Society." Dr. Barron also delivered an address before the Minnesota Academy of Medicine, at Minneapolis, on "Importance

of Hepatomegaly and Splenomegaly in Differential Diagnosis."

At the annual meeting of the Medical Society of Pennsylvania, October 5-8 at Scranton, Pa., the following officers were elected:

Dr. William H. Mayer (Fellow), Pittsburgh, President;

Dr. Charles Falkowsky, Jr. (Fellow), Scranton, President-Elect;

Dr. Walter F. Donaldson (Fellow), Pittsburgh, Secretary.

Dr. Anton J. Carlson (Fellow), Professor of Physiology at the University of Chicago, delivered the third annual William T. Belfield Lecture of the Chicago Urological Society on October 29, in the auditorium of the Medical and Dental Arts Bldg. Dr. Carlson's subject was "Rejuvenation."

Dr. Andrew B. Rivers (Fellow), Rochester, Minn., addressed the 46th semiannual meeting of the Eleventh Indiana Councilor District Medical Association, October 15, on "Cause of Hematemesis."

Dr. Harry Gauss (Fellow), Denver, Colo., spoke on "Nervous Indigestion" at the sixty-first annual meeting of the Colorado State Medical Society, September 16. On October 27, he was a guest speaker at the forty-fifth annual meeting of the Colorado Homeopathic Society, where he delivered an address on "The Basis of Diet."

Dr. Gauss also was a guest speaker at the seventh annual meeting of the Colorado Hospital Association held jointly with the Colorado Dietetics Association, where he spoke on "The History of Diet in Fever."

Doctors Willis F. Manges (Fellow), Philadelphia, E. J. G. Beardsley (Governor and Fellow), Philadelphia, and H. L. Tonkin (Associate), Williamsport, addressed the Lycoming County (Pa.) Medical Society at the Annual Clinic of the society at the Williamsport Hospital on November 13.

Dr. George A. Harrop, Jr. (Fellow), Baltimore, addressed the Baltimore City Medical Society, October 23, on "Treatment

of Addison's Disease with Adrenal Cortical Hormone."

Dr. Howard R. Hartman (Fellow), Rochester, Minn., recently delivered one of the second annual series of graduate lectures offered to physicians of Northampton, Pa., and surrounding counties under the auspices of the Easton Hospital. Dr. Hartman's subject was "Gastric Lesions and Gastric Hemorrhage."

Dr. William H. Mayer (Fellow), Pittsburgh, delivered an address, October 15, on "Fundamentals of the Mental Hygiene Problem" before the Cambria County Medical Society at Johnstown, Pa.

Dr. Horton R. Casparis (Fellow), Nashville, Tenn., discussed "Sinus Conditions in Childhood" before the Chattanooga and Hamilton County (Tenn.) Medical Association, October 8.

Lieut. Comdr. Franklin F. Murdoch (Fellow) has been appointed Professor of Tropical Medicine at the George Washington University School of Medicine.

Dr. James H. Hutton (Associate), Chicago, addressed the La Salle County (Ill.) Medical Society, October 27, on "Recent Advances in Endocrinology."

Dr. Bayard T. Horton (Fellow), Rochester, Minn., spoke on "Buerger's Disease," before the Stephenson County (Ill.) Medical Society on October 15.

Dr. Oscar W. Bethea (Fellow), New Orleans, La., recently addressed the Lafourche Parish Medical Society on "Recent Advances in Diagnosis."

"Histamine in the Study of Gastric Secretion and Disorders of the Stomach" was the title of an address delivered before the Kalamazoo Academy of Medicine, October 20, by Dr. Charles L. Brown (Fellow), Ann Arbor, Mich.

Dr. George L. Lambright (Fellow), Cleveland, addressed the Cleveland Academy

of Medicine, October 16, on "The Problem of Arthritis."

Dr. Frank Smithies (Master), Chicago, Ill., addressed the Mahoning County (Ohio) Medical Society at Youngstown, October 27, on "Gastrorrhagia—Its Pathological and Clinical Significance and its Management."

Dr. Frederick G. Banting (Fellow), Professor of Medical Research at the University of Toronto Faculty of Medicine was the recipient of the honorary degree of Doctor of Science at the annual convocation of the University of the State of New York at Albany, October 15.

The eighty-fifth semiannual meeting of the Southern California Medical Association was held at Hollywood, Calif., November 13-14, under the presidency of Dr. Fred B. Clarke (Fellow), Long Beach. The following Fellows of the College delivered papers as indicated below:

Dr. Samuel Ayres, Jr., Los Angeles—
"Use of the Patch Test in the Diagnosis of Contact Dermatitis;"

Dr. Raymond G. Taylor, Los Angeles—
"Some of the Causes of Failure in Treatment of Cancer."

Dr. J. Curtis Lyter (Fellow), St. Louis, addressed the Randolph County (Ill.) Medical Society, October 20, on diagnosis and treatment of diseases of the heart.

On October 28, Dr. James B. Herrick (Fellow), Chicago, addressed the Medical History Club of the University of Illinois College of Medicine. Dr. Herrick's subject was "Auenbrugger and Laennec."

Dr. Harold W. Palmer (Associate), Wichita, Kansas, spoke on "Hypothyroid States" before the October 20 meeting of the Sedgwick County (Kansas), Medical Society.

Dr. Sidney A. Slater (Fellow), Worthington, Minn., was recently elected President of the Southwestern Minnesota Medical Association.

Dr. Thomas Grier Miller (Fellow), Philadelphia, addressed the Atlantic County Medical Society at Atlantic City, N. J., October 9, on "Diagnosis and Management of the More Common Diseases of the Digestive System."

Dr. Anthony Bassler (Fellow), New York, N. Y., is Vice President of the New York Physicians' Club, a social organization which was recently organized.

Dr. Frank A. Evans (Fellow), Pittsburgh, Pa., was one of the speakers on the program of the Allegheny County Medical Society, held at Pittsburgh on October 27. Dr. Evans' subject was "Infectious Mononucleosis."

Dr. Ray M. Balyeat (Fellow), Oklahoma City, Okla., addressed the Third District Medical Society at Lubbock, Texas, October 27-28, on "Allergic Migraine—Diagnosis and Treatment."

The following Fellows of the College addressed the forty-second annual meeting of the Association of American Medical Colleges, which was held in New Orleans, November 30-December 2:

Dr. Percy T. Magan, Los Angeles—
"Role of the Medical School in the Development of Character in the Medical Student;"

Dr. David J. Davis, Chicago—"Cooperation between the College of Medicine of the State University and Other State Departments in Illinois;"

Dr. Waller S. Leathers, Nashville—
"Teaching of Preventive Medicine;"

Dr. Horton R. Casparis, Nashville—
"Pediatrics: Place in General Health Education Program."

Dr. Kenneth S. Davis (Fellow), Los Angeles, addressed the Los Angeles County Medical Association, November 5, on "Sarcoma of the Stomach."

Dr. Charles A. Elliott (Fellow), Chicago, was among the speakers on the program of the fifty-seventh annual meeting of the Southern Illinois Medical Association, No-

vember 5-6. Dr. Elliott spoke on "Management of Edema."

Dr. Chester S. Keefer (Fellow), Boston, Mass., appeared on the clinical program of the joint meeting of the Suffolk District Medical Society and the Boston Medical Library on November 18. Dr. Keefer's subject was "Importance of Infection in Arthritis."

Dr. Bernard Fantus (Fellow), Chicago, spoke before the joint meeting of the Saginaw and Bay County (Michigan) Medical Societies, October 28, on "Therapy of Colonic Stasis."

Dr. James F. Rooney (Fellow), Albany, N. Y., addressed the eighth district branch of the Medical Society of the State of New York, October 1, on "Coronary Thrombosis."

Dr. J. H. Elliott (Governor and Fellow), Toronto, has been appointed Professor of History of Medicine at the University of Toronto.

Dr. Henry S. Houghton (Fellow), Dean of the State University of Iowa College of Medicine, is now on tour of the Orient as a member of a commission appointed to appraise and evaluate facts on foreign missions.

Dr. Joseph H. Pratt (Fellow), Boston, has been appointed one of the associates of the Bingham Fund Associates for the Advancement of Rural Medicine, founded by Mr. William Bingham, 2nd, of Bethel, Maine, for the purpose of giving aid to the development of medical practice in the State of Maine, and to provide a fund for the advancement of rural medicine.

Dr. L. Winfield Kohn (Fellow), New York City, acted as Chairman of a meeting of the Baltimore Medical Club of New York, held at the New York Academy of Medicine Building on November 12.

Dr. J. M. T. Finney, Professor of Clinical Surgery at Johns Hopkins School of Medicine, and Dr. Julius Friedenwald (Fel-

low), Professor of Gastro-enterology at the University of Maryland School of Medicine, were the guest speakers.

Dr. Gerald B. Webb (Fellow), Colorado Springs, Colo., delivered a lecture on "The Prescription of Literature," October 21, in connection with a series of lectures on "The Care of the Patient" at the Harvard University Medical School.

Dr. Stewart R. Roberts (Fellow), Atlanta, Ga., gave the second lecture of the series on October 28, his title being, "The Art and Human Nature."

Dr. William W. Duke (Fellow), Kansas City, delivered an address on allergy, October 13, in connection with the semiannual meeting of the Fort Worth Medical and Surgical Clinics and the meeting of the Northwest Texas District Medical Society.

Dr. Frank N. Wilson and Dr. Carl V. Weller (Fellows) were among those who assisted in the graduate course arranged by the Department of Postgraduate Medicine of the University of Michigan Medical School and the Michigan State Medical Society, November 3-7. Diseases of the heart and circulatory systems were considered.

Dr. Weller has recently been elected president of the newly organized Michigan State Pathological Society.

Dr. Ralph Pemberton (Fellow), Philadelphia, addressed the Jackson County (Mich.) Medical Society at their meeting in Jackson, November 5, on "Arthritis."

The following appointments and promotions at the Long Island College of Medicine, New York City, were announced recently:

Dr. Frank B. Cross (Fellow)—Clinical Medicine;

Dr. Daniel M. McCarthy (Fellow), Assistant Clinical Professor of Medicine;

Dr. Paul L. Parrish (Fellow), and Dr. Murray B. Gordon (Fellow) promoted to Professors of Clinical Pediatrics.

Dr. H. Sheridan Baketel (Fellow), Jersey City, N. J., has become Professor Emeritus of Preventive Medicine and Hygiene.

Dr. Egerton L. Crispin (Fellow), Los Angeles, and Dr. Porter P. Vinson (Fellow), Rochester, Minn., were elected President and Treasurer, respectively, of the Association of Resident and Ex-Resident Physicians of the Mayo Clinic and Mayo Foundation at the thirteenth annual reunion of this body in Rochester, October 9.

A series of public lectures in the interest of public health education will be offered under the auspices of the Medical Society of the District of Columbia during the fall and winter months. Dr. James P. Leake (Fellow) of the U. S. Public Health Service, delivered the first lecture, October 25, on "Infantile Paralysis." Dr. William A. White (Fellow), Washington, delivered the next lecture, November 8, on "Mental Health," and Dr. Wallace M. Yater (Fellow), Washington, delivered the third lecture, December 6, on "Physical Fitness at Fifty."

Dr. Henry C. Macatee (Fellow), Washington, was a speaker at a symposium on "When Winter Comes," in connection with these lectures, on November 22.

Dr. Louis H. Fligman (Fellow), Helena, State Director of the American Society for the Control of Cancer, and Dr. Ernest D. Hitchcock (Fellow), Great Falls, have been appointed Chairman and a member, respectively, of a Committee of fifteen members of the State Medical Society of Montana for the purpose of formulating plans for an active campaign against cancer in that State.

Dr. Alfred Stengel (Master), Vice President of the University of Pennsylvania, Philadelphia, delivered an address on "Physical Diagnosis in Relation to Circulatory Conditions" before the meeting of the Association of Surgeons of the Pennsylvania Railroad, October 9, in New York City.

GIFTS TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

Acknowledgment is made of the receipt from Dr. Edward J. Stieglitz (Fellow), Chicago, of his book "Arterial Hypertension," and of the receipt of a printed copy of a radio address entitled "Government Interference in the Home," delivered by Dr. William Gerry Morgan (Fellow), Washington, D. C., on Sunday, November 15, 1931, over the network of the National Broadcasting Company.

The following gifts of reprints by members to the College Library are acknowledged:

- Dr. Linn J. Boyd (Fellow), New York, N. Y.—1 reprint;
- Dr. L. Winfield Kohn (Fellow), New York, N. Y.—11 reprints;
- Dr. William H. Kraemer (Fellow), Wilmington, Del.—1 reprint;
- Dr. Philip B. Matz (Fellow), Washington, D. C.—1 reprint;
- Dr. Roy D. Metz (Associate), Detroit, Mich.—1 reprint;
- Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint;
- Dr. Robert E. Ramsay (Fellow), Pasadena, Calif.—1 reprint;
- Dr. Audley O. Sanders (Fellow), Palo Alto, Calif.—5 reprints;
- Dr. Walter M. Simpson (Fellow), Dayton, Ohio—1 reprint;
- Dr. Carl Vischer (Fellow), Philadelphia, Pa.—1 reprint;
- Dr. Frank Wright (Fellow), Chicago, Ill.—1 reprint.

Dr. John E. Gordon (Fellow), Detroit, presented a paper on "Clinical Aspects of Poliomyelitis" before the Gratiot-Isabella-Clare County Medical Society, September 17.

Dr. James P. Leake (Fellow), U. S. Public Health Service, was one of the speakers at a symposium on the after-care of poliomyelitis under the auspices of the Bronx County (New York) Medical Society, September 16.

Dr. Ray W. Kissane (Fellow), Columbus, Ohio, used as his title "Relation of Per-

sonal Habits to Adult Heart Disease" in an address before the Knox County Medical Society at Mt. Vernon, Ohio, September 24.

The Fayette County (Pa.) Medical Society held its meeting at Uniontown, October 22. The following Fellows of the College conducted clinics:

- Dr. Henry L. Bockus, Philadelphia—Gastro-enterology;
- Dr. George Morris Piersol, Philadelphia—Internal Medicine;
- Dr. Harry B. Wilmer, Philadelphia—Allergic Diseases;
- Dr. John Eiman, Philadelphia—Pathology.

Dr. Elmer H. Funk (Fellow), Philadelphia, was recently appointed to the Sutherland M. Prevost Chair of Therapeutics, Materia Medica and Diagnosis at the Jefferson Medical College, succeeding the late Dr. Hobart Amory Hare.

Dr. Robert B. Wood (Fellow), Knoxville, Tenn., addressed the Hamblen County Medical Society, recently, on "Metabolism and Hypertension".

Dr. Wood also addressed the Roane, McMinn, Monroe and Loudon County Medical Society in Lenoir City, September 3, on "Myocardial Failure".

Dr. Ray C. Blankinship (Fellow), Madison, Wis., addressed the Waupaca County Medical Association at Clintonville, September 24, on "Gastrointestinal Conditions."

Dr. Arthur L. Bloomfield (Fellow), Professor of Medicine, Stanford University School of Medicine, San Francisco, presented the opening lecture of the University of Southern California, September 15; his subject being, "Some Current Problems in Medical Education".

Dr. Lorenz W. Frank (Fellow), Denver, is the Constitutional Secretary of the Colorado State Medical Society.

Dr. James G. Carr (Fellow), Chicago, addressed the Morgan County (Ill.) Medi-

cal Society, September 10, on "Rheumatic Heart Disease".

Dr. Ray G. Barrick (Associate), formerly Assistant Professor of Psychiatry at the State University of Iowa College of Medicine, has accepted an appointment at the Institute of Juvenile Research, Chicago. Dr. Barrick will be in a charge of mental health work at the Illinois State Penitentiary, Assistant Professor of Criminology at the University of Illinois College of Medicine and Psychiatrist at the Joliet Child Guidance Clinic.

Dr. Robert A. Cooke (Fellow), New York City, addressed the joint sessions of the Omaha-Douglas County (Nebr.) Medical Society and the American Congress on Physical Therapy, October 7, on allergy.

Dr. Clarence H. Beecher (Fellow), Burlington, Vt., addressed the Grafton County (N. H.), Medical Society in a co-operative meeting with Dartmouth Medical School, October 9, on "Clinical Use of Purgatives".

Dr. Joseph H. Barach (Fellow), Pittsburgh, is the Director of the recently dedicated Falk Clinic of the University of Pittsburgh. The Clinic was dedicated on September 28. Doctors Willard J. Stone (Fellow), Pasadena, and Dr. Alfred Stengel (Master), Philadelphia, were guests of honor and speakers at the evening meeting, Dr. Stone's title being "Certain Economic Phases of Medical Practice" and Dr. Stengel's title being "The Clinic and Medical Development". Dr. Barach spoke upon "Aims of the Falk Clinic".

Dr. Frederick G. Speidel (Associate), Louisville, Ky., participated in a symposium on diabetes conducted before the Jefferson County Medical Society, September 21.

Dr. Hans Lissner (Fellow), San Francisco, addressed the 57th annual session of the Oregon State Medical Society at Eugene, Oregon, September 24, on "Recent Discoveries in Endocrinology and their Clinical Application".

Dr. Horton Casparis (Fellow), Nashville, Tenn., Dr. Francis H. Smith (Fellow), Abingdon, Va., and Dr. George B. Lawson (Fellow), Roanoke, Va., all delivered papers before the Southwestern Virginia Medical Society at Marion, Va., September 24-25.

At the 32nd annual meeting of the American Roentgen Ray Society at Atlantic City, September 22-25, the following Fellows participated as indicated:

Dr. Willis F. Manges, Philadelphia—"Primary Carcinoma of the Lung—Roentgen Ray Diagnosis and Preliminary Report on Roentgen Therapy"; Dr. Byrl R. Kirklin, Rochester, Minn., (with Dr. C. M. Moore)—"Benign Giant Cell Tumors".

Rear Admiral Edward R. Stitt (Fellow), formerly Surgeon General of the U. S. Navy, was retired from active duty in the U. S. Navy October 1.

Lieut. Comdr. John H. Chambers (Fellow), Medical Corps of the U. S. Navy, has been transferred from the Public Health Service of Haiti to the Naval Hospital, League Island, Philadelphia.

Dr. Francis E. Sencar (Fellow), Chicago, conducted a dermatologic clinic in connection with the Logan County Medical Society's meeting at Lincoln, Ill., September 24.

Dr. William W. Duke (Fellow), Kansas City, Mo., delivered a paper on "Allergy as Related to General Medicine" before the Dubuque County (Iowa) Medical Society, September 8.

Dr. S. Marx White (Fellow and President), Minneapolis, addressed the Linn County (Iowa) Medical Society at Cedar Rapids, September 10, on "Subacute Bacterial Endocarditis".

Dr. Philip F. Barbour (Fellow), Louisville, Ky., was elected President-Elect of the Kentucky State Medical Association at its annual meeting at Lexington, September 7-10.

Dr. Stuart Pritchard (Fellow), Battle Creek, and Dr. James D. Bruce (Fellow), Ann Arbor, were among those chosen by Governor Brucker as members of an Advisory Commission to coordinate child welfare work in Michigan.

Dr. Frederick G. Banting (Fellow), Toronto, was one of the speakers at the annual convocation of the University of the State of New York, held in the State Education Building, Albany, October 15-16.

Dr. I. M. Rabinowitch (Fellow), Montreal, participated in the symposium on the liver and spleen, held under the auspices of the Vermont State Medical Society at Rutland, October 8-9.

Dr. Louis F. Jermain and Dr. John J. McGovern (Fellows), both of Milwaukee, were the recipients of the gold seal of the Wisconsin Medical Society at its recent annual meeting. The gold seal is an honorary award presented annually.

Dr. Otho R. Fiedler (Fellow), Sheboygan, was installed as President of the Society for the coming year.

OBITUARIES

DR. BRADFORD CHURCHILL
LOVELAND

Dr. BRADFORD CHURCHILL LOVE-
LAND (Fellow), Syracuse, N. Y., died
June 25, 1931, of myocarditis; age
sixty-nine years.

Dr. Loveland was born at Newark,
N. Y., and attended Newark Acade-
my, Susquehanna University, and
later the University of Michigan Med-
ical School, from which he received
the degree of Doctor of Medicine in
1888. He pursued postgraduate study
at the New York Post-Graduate Med-
ical School. He was a lecturer on
medical jurisprudence at the Syracuse
University School of Law from 1917
to 1927. His practice was limited to
neurology and psychiatry. During
1898-1899 he served as Medical Su-
perintendent of the Clifton Springs
Sanitarium. Soon thereafter he went
to Syracuse, where he became Neu-
rologist for the Hospital of the Good
Shepherd and the Syracuse Free Dis-
pensary. For several years he served
as Chief of the Bureau of Psychiatry
of the Syracuse Department of
Health, and was Neurologist to the
Syracuse University Hospital. Dr.
Loveland was a member and trustee
of the Syracuse Academy of Medi-
cine, a member of the Onodaga Med-
ical Society, a member of the New

York State Medical Association, a
Fellow of the American Medical As-
sociation, and had been a Fellow of
the American College of Physicians
since April 15, 1920. He was the
author of a considerable number of
articles published in various medical
journals.

DR. THEODORE LEACRAFT
HEIN

Dr. THEODORE LEACRAFT HEIN
(Associate), New York City, died
September 25, 1931, of heart disease;
aged 52 years.

Dr. Hein was a graduate of the Col-
lege of Physicians and Surgeons of
Columbia University, 1905. He did
postgraduate study in medicine at St.
Bartholomews, London; Charité of
Berlin, and at the Allgemeines Kran-
kenhaus of Vienna. He was formerly
instructor at the New York Post-
graduate Hospital, and assistant in the
Vanderbilt Clinic and the Stuyvesant
Policlinic. At the time of his death,
he was physician-in-charge to the
Queens Plaza and Ridgewood Clinics,
Department of Health. Dr. Hein was
a Fellow of the American Medical
Association, a member of the Medical
Society of the County of New York,
and had been an Associate of the Col-
lege since 1921.